Efficacy and Feasibility of Fully Automated Closed Loop Insulin Pump Therapy after Islet Auto-Transplantation

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Dedication

This thesis is dedicated to the two wonderful ladies in my life, my wife Tania and our daughter Olympia.

Abstract

Background: Total pancreatectomy with islet auto-transplantation (TPIAT) may be performed for patients with unrelenting chronic pancreatitis to relieve pain while minimizing the risk of diabetes. Avoidance of hyperglycemia is essential after TPIAT to minimize beta cell apoptosis during islet engraftment. Closed loop (CL) therapy has never previously been investigated in islet transplant recipients but CL devices may improve glycemic control within a narrow therapeutic target. Our objective is to determine the feasibility and efficacy of CL therapy to maintain glucose profiles close to normoglycemia following TPIAT.

Methods: Here we present analysis of 14 patients (36% male; mean age 35.9±11.4 years-old). At the time of transition from IV to subcutaneous insulin (POD=6±1.4 days), subjects were block randomized to subcutaneous insulin via a CL pump (n=7) or multiple daily injections (n=7) for 72 hours.

Results: Mean serum glucose values were significantly lower in the experimental group than in the control group (111±4 mg/dL v. 130±13 mg/dL; p=0.003). Glycemic variability was also lower in the experimental group than in the control group based on standard deviation (14.1±3.3 mg/dL v. 21.0±10.2 mg/dL; p=0.115), though was not statistically significant. Hyperglycemia and hypoglycemia AUC were less in the experimental group than in the control group, though did not meet criteria for statistical significance: 2025±1177 v. 7860±11444 min*mg/dL; p=0.2045 and 146±270 v. 1615±4267 min*mg/dL; p=0.3813, respectively.

Discussion: Results from this study show that CL therapy is superior to conventional therapy in maintaining euglycemia without increased hypoglycemia. This technology shows significant promise as a tool to maintain strict euglycemic targets and minimize hypoglycemia after TPIAT.

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1.0 INTRODUCTION

1.1 Chronic Pancreatitis

Chronic pancreatitis (CP) is an irreversible condition whereby chronic or recurrent pancreatic inflammation, fibrosis and scarring damage both the exocrine and endocrine functions of the pancreas. CP is characterized by chronic or recurrent abdominal pain, often leading to narcotic dependence and limitations in activities of daily living. First-line interventions consist of medical procedures such as endoscopic retrograde cholangio-pancreatography (ERCP) with sphincterotomy, endoscopic balloon dilation, or stent placement. If these procedures are unsuccessful in relieving pain and improving quality of life, then removal of the pancreas, total pancreatectomy (TP), may be considered. Such a procedure however would result in inevitable post-surgical diabetes as the insulin producing islet cells would be removed along with the exocrine portion of the pancreas. A simultaneous islet auto-transplantation (IAT) may prevent or minimize post-surgical diabetes by restoring all or some of the endocrine function of the excised pancreas.

The incidence of CP is estimated at around 4 cases per 100,000 person-years and the prevalence is about 4 cases per 10,000 persons or a total prevalence of 0.04-5% of the adult population [1, 2]. While CP is seen in both genders it is more common in men by a ratio of 4.6:1 [3]. Alcohol has long been identified as the most common cause of CP contributing to 70-80% of cases among the adult population [2, 4, 5]. More recently, smoking has become recognized as an important independent risk factor and disease modifier providing a synergistic effect with alcohol use [3, 4, 6]. The second most common cause of CP is idiopathic pancreatitis. Hereditary or genetic pancreatitis is the third most common cause overall and accounts for a majority of cases in the pediatric population [7, 8]. The most common genetic causes are mutations to the cationic trypsinogen gene (PRSS1), various Cystic Fibrosis Transmembrane Regulator (CFTR) mutations and serine protease inhibitor, Kazal type 1 (SPINK1) mutations [7, 9, 10]. Patients with hereditary or

genetic pancreatitis are at particularly high lifetime risk for significant complications including 37.2% chance of exocrine failure, 47.6% chance of endocrine failure and 44.0% chance of pancreatic cancer [10].

Initial presentation of pancreatitis is often progressive episodes of recurrent abdominal pain. The disease process can be thought of as a progressive spectrum from acute pancreatitis to recurrent pancreatitis to chronic pancreatitis [11]. The pancreatic enzymes of amylase and lipase are usually significantly elevated in the acute phases, though their levels may fall with disease progression to chronic pancreatitis as fibrotic tissue replaces normal exocrine tissue [2, 5]. Diagnosis and classification of chronic pancreatitis can be challenging and there exists substantial debate in the published literature on the appropriate methods and criteria [12-15]. Frequently used imaging modalities include computerized tomography (CT) of the abdomen, magnetic resonance cholangiopancreatography (MRCP), ERCP, and endoscopic ultrasound (EUS). At the University of Minnesota (UMN) the diagnosis of CP is made based on clinical history and imaging evidence (calcification on CT scan, ductal abnormalities on MRCP or ERCP and/or EUS), and supported by genetic confirmation with PRSS1, SPINK1, and CFTR testing in the pediatric population and in cases where familial causes are suspected [16].

First-line interventions for CP consist of medical management with narcotics and medical procedures such as ERCP with sphincterotomy, endoscopic balloon dilation, or stent placement [11]. In patients for whom these interventions are unsuccessful at relieving pain and improving quality of life, TP may be considered to remove the insulting exocrine pancreas along with simultaneous IAT to prevent post-surgical diabetes in a combined total pancreatectomy with islet auto-transplantation (TPIAT) procedure.

1.2 TPIAT

The first ever human TPIAT was performed by Dr. David Sutherland at UMN in 1977 [17]. Since then over 600 TPIAT procedures have been performed at UMN, making it the largest center in the world for this highly specialized procedure [18]. Approximately 4-6 TPIAT's are performed per month. As with all surgical procedures, pre-and post-surgical management plays a vital role in producing successful patient outcomes. Potential candidates for surgery are evaluated by a multidisciplinary team using the published UMN criteria for TPIAT (Table 1.) [16].

Table 1. University of Minnesota Criteria for Total Pancreatectomy and Islet Auto-Transplantation[16]

Patient Must Fulfill Criteria Numbers 1-5:

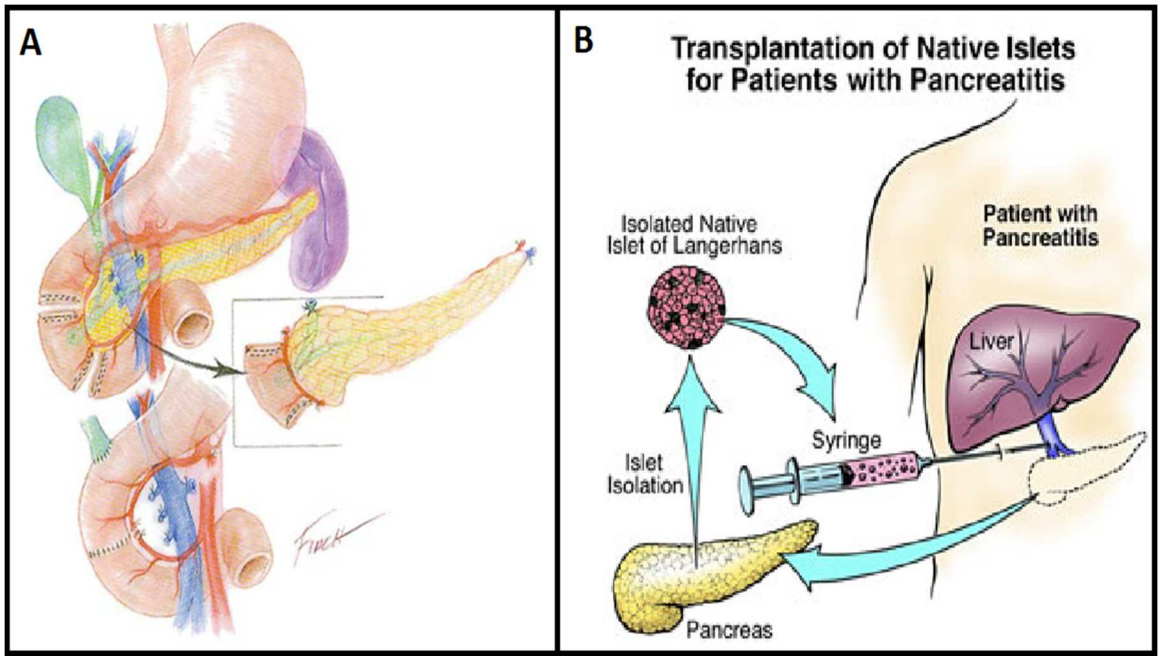
1. Diagnosis of chronic pancreatitis, based on chronic abdominal pain of >6 months duration and at least 1 of the following:
   - Pancreatic calcifications on CT scan.
   - At least 2 of the following: ≥4/9 critieria on EUS, compatible ductal or parenchymal abnormalities on secretin MRCP; abnormal endoscopic pancreatic function tests (peak HCO_2 ≤80 mmol/L)
   - Histopathology confirmed diagnosis of chronic pancreatitis
   - Compatible clinical history and documented hereditary pancreatitis (PRSS1 gene mutation)
   - History of recurrent acute pancreatitis (more than 1 episode of characteristic pain associated with imaging diagnostic of acute pancreatitis and/or elevated serum amylase or lipase >3 times upper limit of normal)
2. At Least 1 of the following:
   - Daily narcotic dependence
   - Pain resulting in impaired quality of life, which may include: inability to attend work/school, recurrent hospitalizations or inability to participate in usual, age-appropriate activities
3. Complete evaluation with no reversible cause of pancreatitis present or untreated
4. Failure to respond to maximal medical and endoscopic therapy
5. Adequate islet cell function (nondiabetic or C-peptide positive)

CT, computerized tomography; EUS, endoscopic ultrasound; MRCP magnetic resonance cholangiopancreatogram

The surgical procedure for TPIAT may vary by case, but generally involves partial duodenectomy, Roux-en-Y duodenojejunostomy, choledochojejunostomy, and splenectomy as described in previous surgical literature from UMN (Figure 1.A.) [19-23]. TP is performed in such a

way that the blood supply to the pancreas is preserved until just prior to removal to minimize warm ischemic time to the islets [22]. In addition patients receive a cholecystectomy and appendectomy if not previously done. Patients also generally receive gastric and jejunal (G-J) tube placement for post-surgical trans-pyloric feeding.

Figure 1. A. Total Pancreatectomy Surgical Procedure involving involves partial duodenectomy, Roux-en-Y duodenojejunostomy, and choledochojejunostomy [21]; B. Total Pancreatectomy with Islet Auto-Transplantation involving islet isolation and infusion into the portal vein [23]



Following removal of the pancreas, a collagenase-based enzyme solution is used to digest the exocrine pancreas, and the remaining islets are harvested via an automated method. The islets are then infused back into the portal vein where they engraft in the liver sinusoids (Figure 1. B.).

Immediately following surgery, patients are started on an intravenous (IV) insulin infusion, titrated to maintain blood glucose (BG) in a narrow range of 80-125 mg/dL. Post-surgical

feeding is begun via Jejunal-tube (J tube) around post-op day #1 at a trophic rate and then titrated up to goal rate gradually as clinically tolerated. Patients are transitioned from IV to subcutaneous (SQ) insulin once they are stable at their goal feeding rate.

Outcomes after TPIAT have been reported in the literature from UMN after >400 successful cases were performed [22]. Pain-improvement was reported in 85% of patients with 59% ceasing narcotic use by 2 years post-surgery. Significant quality of life improvement was shown from baseline in all dimensions of function. At 3 years post-surgery 30% of patients were insulin-independent with an additional 33% having partial islet function. While no single factor is predictive of insulin independence, islet equivalents (IEq) transplanted has been shown to be the main predictor of future insulin independence [19]. Among patients from UMN, insulin independence at 1 year post-transplant was observed in 63% of patients receiving > 5000 IEq/kg, 27% of those receiving 2501-5000 IEq/kg and 7% of those receiving ≤ 2500 IEq/kg.

1.3 Islet Engraftment

During islet isolation, purification and harvesting, islets are stripped of their native arteriolar blood supply. In the immediate post-transplant period, islets are reliant on diffusion of nutrients and oxygen to the islet core until neovascularization is complete, a process that may take weeks to months [24, 25]. During this engraftment period, the transplanted islets are especially vulnerable to overstimulation by hyperglycemia in an anoxic environment, which contributes to beta-cell loss [26, 27]. Studies in animal models have demonstrated that hyperglycemia increases beta-cell apoptosis, while maintenance of narrow-range euglycemia reduces the IEq necessary to prevent post-surgical diabetes [28-33]. Data from a large TPIAT cohort at UMN further supports these experimental findings by showing that small differences in mean blood glucose in the first week post-transplant correlate with later insulin independence [34].

1.4 Insulin Pump Technology and Closing the Loop

Use of portable subcutaneous insulin infusion pumps first became possible in the late 1970's, with early studies showing the possibility of improved glycemic control with this technology [35]. With the publication of the primary results from the Diabetes Control and Complications Trial in 1993 [36], there was renewed focus on the importance of maintaining near-normal blood glucose control and reducing hemoglobin A1c to minimize the potential for micro and macrovascular complications. However achievement of these glycemic parameters came at the cost of increased frequency of hypoglycemic events.

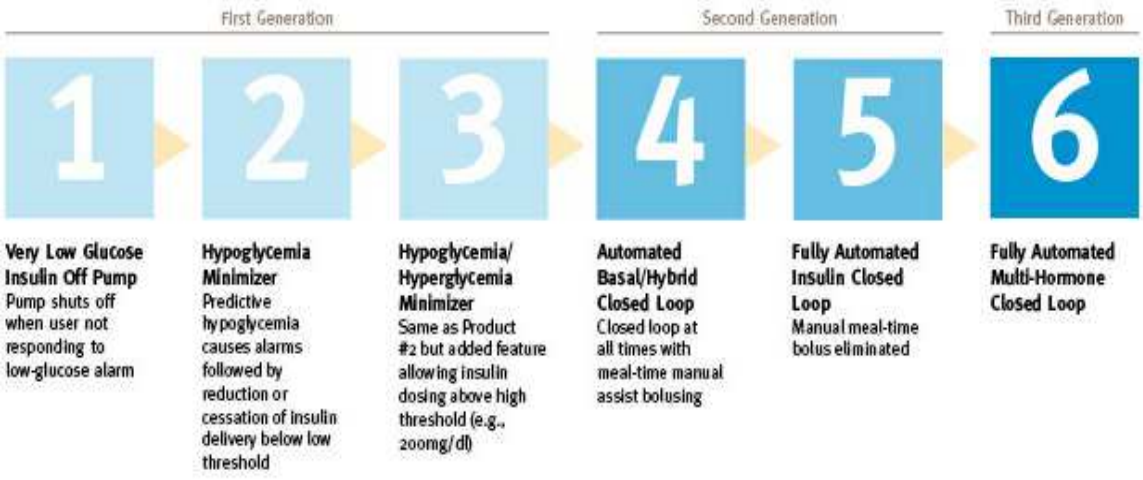
Over the next decade this shift in care promoted commercial development of synthetic insulin analogues for improved multiple daily injection (MDI) therapy such as long-acting insulin glargine (Lantus) and rapid-acting insulin aspart (Novolog) and insulin lispro (Humalog). During this same period there was rapid expansion in interest and design of feasible Continuous Subcutaneous Insulin Infusion (CSII) systems which gained wide-spread commercial acceptance in the late 1990's and early 2000's as early research supported improved outcomes with pump usage [37].

The concept of a mechanical artificial pancreas (AP) has followed development of CSII technology. Such a system would involve the components of a continuous insulin delivery device, glucose sensor, control tool decision algorithm(s) and any additional devices necessary for communication between these components. This type of approach would allow for automated control of blood glucose levels, minimizing periods of hyperglycemia but also importantly reducing the risk for hypoglycemia. While there have been those in the research community with interest in intravenous sampling of blood glucose and/or delivery of insulin, the majority of doctors in the clinical community view a subcutaneous approach for SQ BG sensing and insulin administration as the only reasonable option likely to gain widespread patient acceptance and usage. This view fueled the development of Continuous Glucose Monitoring (CGM) devices

during the 1980's and 1990's with first commercial approval of a CGM device in 1999 [38-41].

In 2006, the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas project outlined a step-wise roadmap to development, refinement and regulatory approval of a SQ/SQ AP system (Figure 2.) [42]. This roadmap describes successive steps from sensor augmented pump (SAP) therapy, first generation systems involving sensor assisted therapy at BG extremes, second generation systems of hybrid and full closed loop therapy and possible third generation systems of multi-hormone (e.g. insulin and glucagon) therapy [43].

Figure 2. Juvenile Diabetes Research Foundation Artificial Pancreas Project Roadmap [42]



At the present time a step-1 commercial device (the Medtronic 530g system) with Threshold Suspend (TS) is available in the United States for patients with overnight hypoglycemia and a recent phase 4 study shows that this system is successful in reducing overnight hypoglycemic events without producing rebound hyperglycemia [44]. A step-2 commercial device (the Medtronic 640g system) with predictive low-glucose suspend was recently approved by the FDA and will be available to patients by the end of 2015. Initial studies

on this technology have shown substantial reduction in overnight hypoglycemia [45, 46]. Step-3 devices with combined hypoglycemia and hyperglycemia minimizers are currently under phase 3 study [47].

Second and third generation devices consisting of hybrid closed loop systems, fully automated closed loop systems and dual-hormonal systems are all under development at various stages of clinical testing at roughly a dozen centers around the world. The pathway to commercial approval for these advanced devices generally occurs in the steps of *in silico* testing using computer based compartment models of glucose response to insulin, followed by testing in hospitalized patients, followed by testing in controlled environment outside the hospital, and finally testing in the home and outpatient environments. Closed loop systems also generally perform better during periods of fasting (such as overnight) and still have difficulty with the glycemic excursion of unannounced meals.

Current research on CL systems demonstrates an overall common theme of successful control of overnight BG with values in target range 70-100% of the time and marked difficulty preventing post-meal glycemic excursions with unannounced meals. An excellent summary article of CL research was recently published by Garg and colleagues [48]. Additional recent studies of importance to the current project are presented below (Table 2.).

Table 2. Summary of Recent Diabetes Technology Studies

Authors	Subjects	Control Type	Setting	Meals	Findings
Breton *et al.* (2012) [49]	38	Control to Range (MPC)	Hospital	Yes	Increased time near normoglycemia from 61 to 74%, reduced hypoglycemia 2.7 fold, improved meal BG without increasing hypoglycemia and achieved 97% near normoglycemia overnight.
Brown *et al.* (2015) [50]	10	DiAs (MPC)	Outpatient	No	CL control overnight significantly improved time in range, reduced mean BG in the AM and overnight and resulted in better control the next day.
Cameron *et al.* (2014) [51]	10	MMPPC (MPC)	Hospital	Yes	With meals the controller maintained reasonable glycemic control with only one controller-induced hypoglycemic event.
Chase *et al.* (2014) [52]	53	MPC	Hospital	Yes	The AP handled 4 different bolus types safely but at the expense of having elevated post-prandial BG in most subjects.
Elleri *et al.* (2012) [53]	8	MPC	Hospital	No	Overnight BG levels were within range 82% of the time when the system was started at 18:00 hours and 64% of the time when started at 21:00 hours.
Elleri *et al.* (2013) [54]	12	MPC	Hospital	Yes	CL control increased time in target range compared to conventional pump therapy (84% v. 49%, p=0.02) without increasing hypoglycemia.
Kovatchev *et al.* (2014) [55]	20	DiAs (MPC)	Outpatient	Yes	CL control reduced hypoglycemia and hypoglycemic treatments compared to SAP therapy. There was a marginal increase in average BG.
Leelarathna *et al.* (2014) [56]	enrolling	MPC	Outpatient	Yes	Outpatient study comparing CL control v. SAP therapy for 3 months. Will aim for 30 participants.
Ly *et al.* (2014) [57]	32	DiAs (MPC)	Outpatient	No	Overnight study at diabetes camp. Median percent time in range was 73% in CL group and 52% for SAP group. Less time in hypoglycemia for CL group than SAP group.
Nimri *et al.* (2014) [58]	24	MD-Logic (FL)	Outpatient	No	CL nights significantly reduced time spent in hypoglycemia and increased time spent in target range compared with SAP therapy.
O'Grady *et al.* (2012) [59]	8	PID	Hospital	No	Time in target range was significantly greater for CL night than open-loop nights. Hypoglycemia was also reduced.
Thabit *et al.* (2015) [60]	40	MPC	Outpatient	No	Used CL overnight and SAP therapy during the day. Improved % time in target with CL therapy compared to control. CL reduced mean BG with no change in variability (SD). Both hyperglycemia and hypoglycemia were reduced.
Zisser *et al.* (2014) [61]	53	MPC	Hospital	Yes	Control-to-range system performed better overnight than during the day with difficulty preventing post-meal BG elevation.

1.5 Control Tool Algorithms

A fundamental aspect of any artificial pancreas system is the control algorithm responsible for making dynamic insulin dosing adjustments in real-time. The theory for artificial pancreas algorithms arises from the discipline of control theory and dynamical systems [62]. Control theory arises from fundamental ideas in mathematics and is a fundamental tool in many engineering

disciplines including Aerospace, Mechanical, Chemical, Electrical and Computer Engineering. An excellent comprehensive review of the engineering of AP algorithms was recently published by Doyle and colleagues in *Diabetes Care* [63].

Different groups around the world are developing 3 different control systems for CL therapy: proportional-integral-derivative control (PID), model predictive control (MPC), and fuzzy logic control (FL). PID control is probably the most basic form of a control system. It calculates proportional error (present error), integral error (past error) and derivative error (predicted future error) and then utilizes a weighted sum to determine insulin dose for that minute [64, 65]. MPC relies on the development of a complex multi-compartment model via a series of differential equations. This model is then used to predict the appropriate dosing action for a fixed time interval (e.g. 15 minutes) after which time the system is reassessed and the appropriate model selected for the next time interval [66]. FL control utilizes a series of "fuzzy" logical decision rules that mimic a human decision maker to make reasoned decisions on diabetes treatment in a manner similar to how a practitioner thinks [67].

The present study utilizes Medtronic's ePID (external physiological insulin delivery) 2.0 controller [64, 65, 68]. This controller uses a modified PID controller with a term for insulin feedback (IFB) previously described in detail by Ruiz *et al.* working with the engineers from Medtronic [68]. Sensor glucose levels at time n ($SG(n)$) are calculated based on a calibration factor (CF; mg/dL/nA) estimated from a linear regression of plasma glucose and filtered sensor current with a fixed sensor delay time of 10 minutes to account for delayed BG shifts between the intravenous and interstitial compartments [69, 70].

$$SG(n) = CF * I_{Filtered}(n) \quad (1)$$

The PID portion of the ePID 2.0 controller utilizes a series of equations outlined below:

$$P(n) = K_p[SG(n) - T_{BG}] \quad (2)$$

$$I(n) = I(n-1) + \frac{K_p}{T_I} * [SG(n) - T_{BG}] \quad (3)$$

$$D(n) = K_p * T_D * \frac{\Delta SG(n)}{\Delta t} \quad (4)$$

$$PID(n) = P(n) + I(n) + D(n) \quad (5)$$

Where K_p is set individually based on the patient's total daily insulin requirement (I_{TDD}; U/day):

$$K_p = \frac{I_{TDD} * 60}{90 * 1500} \quad (6)$$

The integral time constant (T_I) was set at 250 and the derivative time constant (T_D) was set at 50. In these equations, n and $n-1$ denote the most recent time value and the value 1 minute previously, respectively. The term $\frac{\Delta SG(n)}{\Delta t}$ denotes the rate of change of SG. The target BG (T_{BG}) was set by the investigators at either 100 or 110 mg/dL based on clinical situation.

The IFB term comes from the following equations:

$$I_{SC}(n) = \alpha_{11} * I_{SC}(n-1) + \beta_1 * I_D(n-1) \quad (7)$$

$$I_P(n) = \alpha_{21} * I_{SC}(n-1) + \alpha_{22} * I_P(n-1) + \beta_2 * I_D(n-1) \quad (8)$$

$$I_{EFF}(n) = \alpha_{31} * I_{SC}(n-1) + \alpha_{32} * I_P(n-1) + \alpha_{33} * I_{EFF}(n-1) + \beta_3 * I_D(n-1) \quad (9)$$

$$IFB(n) = \gamma_1 * I_{SC}(n) + \gamma_2 * I_P(n) + \gamma_3 * I_{EFF}(n) \quad (10)$$

Here, real-time estimates of subcutaneous insulin (I_{SC}), plasma insulin (I_P), and interstitial/effective insulin (I_{EFF}) concentrations are dependent on one another, scaled using varying α coefficients and are dependent on insulin delivery (I_D). Insulin delivery (I_D) at time n is then determined by the final equation:

$$I_D(n) = (1 + \gamma_1 + \gamma_2 + \gamma_3) * PID(n) - IFB(n) \quad (11)$$

1.6 Potential Impact of the Work on Health

The present study involves several elements of innovation with potential to significantly impact health. This study represents the first use of closed loop insulin technology in an islet transplant population. Demonstration of the ability to safely and effectively achieve ambitious glycemic targets in this population is an important first step towards regulatory approval and clinical acceptance of this new technology. The benefits of narrow range euglycemic control in the post-TPIAT period are improved islet engraftment and long term survival with corresponding decreased long term insulin requirements.

In addition to the potential benefits for the CP population, this work may have impact on the larger type 1 diabetes population. Islet auto-transplantation in CP patients involves a patient with a non-autoimmune condition receiving their own (human) islets following pancreatic removal. In this situation there is no underlying *auto*-immunity, and no risk for *allo*-immune or *xeno*-immune reaction as would be seen for a patient receiving cadaveric donor or porcine donor islets. TPIAT therefore provides a unique human model for the mechanics of islet transplantation and engraftment which lacks *auto*-, *allo*-, or *xeno*-immunity as well as potential toxicity from the medications used to modulate immunity. This population thus presents a novel opportunity to refine the mechanical aspects of islet transplantation with potential to benefit additional patient populations which may require *allo*- or *xeno*-grafts to correct their underlying conditions.

2.0 METHODS

2.1 Pre-Study Objectives and Hypotheses

The following objectives, specific aims and hypotheses were outlined *a priori* as part of the grant applications, FDA application, IRB application and study protocol.

Objectives:

The overall objective of this pilot study was to determine the feasibility and efficacy of closed loop (CL) insulin pump therapy to maintain glucose profiles close to normoglycemia following islet auto-transplantation, during the critical period of islet engraftment. Such a therapy would be beneficial in reducing hyperglycemia-induced beta cell apoptosis and thereby may improve long-term islet transplant outcomes. The primary objective of the pilot proposal was to demonstrate that closed loop pump therapy is superior to conventional subcutaneous insulin at maintaining target blood glucose early after IAT, and to gather preliminary outcomes data on islet function. The results of this study may also be used to plan and support an NIH grant proposal for a larger clinical trial.

Specific Aims:

Specific Aim #1: To determine if use of a closed loop insulin system can successfully achieve tighter glycemic control compared to conventional injection regimens in the early post-transplant period. To investigate this aim, 20 patients will be randomized 1:1 to receive either (1) closed loop pump therapy for 72 hours or (2) standard insulin injection therapy plus a continuous glucose monitor sensor for data collection at the time of transition from intravenous to subcutaneous insulin (~1 week post-transplant).

> ***Hypothesis 1:*** *The mean blood glucose will be lower in the closed loop pump group than in the group receiving conventional therapy*.
>
> ***Hypothesis 2:*** *There will be less glycemic variability in the closed loop pump group, as evidenced by lower standard deviation in blood glucose*

Hypothesis 3: *There will be less time spent in hyperglycemia (>140 mg/dL) and hypoglycemia (<70 mg/dl) in the closed loop pump group. Area Under the Curve (AUC) above 140mg/dl and AUC below 70mg/dl will be less in CL group.*

Specific Aim #2: To collect preliminary data on insulin requirements and islet function in the first 6 months post-transplant in the closed loop pump and conventional therapy group. Although the duration of closed loop pump therapy in this initial pilot study is short, evidence of reduced insulin use and/or higher C-peptide secretion at 6 months post-transplant in this pilot analysis would provide powerful evidence to support a larger trial and a prolonged duration of treatment.

Hypothesis 4: *Insulin requirements (units/kg/day) will be lower and stimulated C-peptide levels from mixed meal testing higher in the closed loop pump group.*

2.2 Patient Population

Participants for the study were patients with chronic pancreatitis being seen by surgeons at the University of Minnesota for evaluation for TPIAT. Potential subjects were approached by a trained member of the study team during part of their multidisciplinary pre-transplant evaluation. Patients were provided with an approved information sheet and sample consent forms for independent review.

Inclusion criteria for participation in the clinical trial were (1) age 21 to 64 years old and (2) undergoing total pancreatectomy and islet auto-transplantation. Exclusion criteria for participation in the trial were (1) preexisting diabetes as defined by ADA criteria for diagnosis of diabetes [71], (2) use of acetaminophen during the 72 hour investigational period due to this medication falsely impacting CGM sensor values, (3) any medical condition requiring corticosteroids, (4) severe psychiatric disease or developmental delays that might interfere with ability to provide informed consent, and (5) any other medical condition which in the opinion of the investigators impairs the person's ability to safely participate in the trial.

Informed consent was obtained during face-to-face consultation with a trained member of the study staff at a separate consent visit during the pre-transplant workup and prior to surgical intervention. Patients were given informational materials and consent forms for review prior to this visit. They were given ample opportunity to ask questions of study staff and all materials were reviewed face-to-face prior to signing any documents. They were informed that participation was optional, they may withdraw consent at any time and failure to participate would not adversely affect their care in anyway.

The clinical trial involved use of an experimental, non-commercially approved medical device in adult patients after surgery for dynamic control of blood glucose. As such, the trial required review and approval by both the University of Minnesota Investigational Review Board (IRB) and the United States Food and Drug Agency (FDA). FDA approval was obtained on August 2nd, 2013 (FDA ID G130178). UMN IRB approval was obtained on October 16th, 2013 (IRB ID 1307M37923). The trial was also registered with clinicaltrials.gov on September 19th, 2013 (ID NCT01945138).

2.3 Randomization

Randomization was performed between the time of informed consent and the day of TPIAT surgery. Participants were block randomized 1:1 to receive subcutaneous insulin via either closed loop insulin pump (experimental arm) or multiple daily injections (control arm). A computer based random number generator was used to generate random number schedules. First, a random number 1-2 was generated with the number 1 representing block size of 2 and the number 2 representing a block size of 4. Then non-repeating random numbers 1-2 or 1-4 were generated based on the block size with odd numbers representing the experimental arm and even numbers representing control arm. A total of 20 assignments were made for each schedule with a 1:1 control to experimental ratio. A total of 5 randomization schedules were prepared. A

physician not otherwise involved with this study was then asked to randomly upload one of the 5 schedules to the randomization module of REDCap. The secure REDCap database was used to house the randomization schedule and to generate the study arm assignment at the time of randomization.

2.4 Timing of Study Visits

Potential participants were first contacted during their pre-transplant evaluation. As part of their routine TPIAT workup participants had a pre-surgical visit at which time baseline labs of hemoglobin A1c, and mixed meal tolerance test (MMTT) with BG and c-peptide levels were obtained (Table 3.). Interested patients were then brought in for a separate consent visit where inclusion and exclusion criteria were reviewed and informed consent was obtained. Randomization was conducted between the time of informed consent and the day of TPIAT surgery. Inclusion and exclusion criteria were reviewed on the day of surgery to ensure that the performed procedure fit with the study definition of TPIAT. Exclusion criteria were again reviewed prior to beginning SQ therapy to ensure that patients were not on acetaminophen or steroids and were stable enough for study participation.

Table 3. Timing of Endpoint Assessment by Study Visit.

Visit	**Hb A1c**	**MMTT**	**C-Peptide**	**BG**	**CGM Data**	**YSI BG Values**	**Insulin Req**
Pre-Surgical	x	x	x	x			
72h Post-Op			x	x	x	x	x
14&28d Post-OP			x	x			
6 month f/u	x	x	x	x			x

When participants reached target continuous J-tube feeds, generally 1 week after surgery, they were converted to either MDI + CGM (control) or CL insulin (experimental) therapy for 72

hours. During this period both groups were evaluated for AM c-peptide and BG levels, q4h reference BG levels (average and standard deviation), CGM BG levels (average, standard deviation, hypoglycemia AUC and % time, and hyperglycemia AUC and % time), and average daily insulin requirements. Participants were also seen for 14 and 28 day post-surgical follow up visits for random c-peptide and laboratory serum glucose evaluation. Participants were then evaluated at 6 months post-TPIAT for laboratory evaluation of hemoglobin A1c, mixed meal tolerance test (serum glucose and c-peptide), and current insulin requirements.

2.5 Study Endpoints

Blood Glucose Values: Blood glucose values were obtained by frequent bedside testing every 30 minutes (± 15 min) during the 72 hour investigational period for the study group, or more often as needed for hyperglycemia or hypoglycemia (as described in safety plan). Testing was performed using a YSI (Yellow Springs Instrument) 2300 STAT Plus Glucose Analyzer. The control group (not on CLP) had blood glucose measured every 4 hours over the 72 hour study period at standard time points (0001, 0400, 0800, 1200, 1600, 2000; ± 15 min) for comparison as would be standard for routine clinical care. Values computed from this data were the **primary endpoint markers of glycemic control: mean blood glucose** and **standard deviation in blood glucose.**

Continuous glucose monitoring (CGM): Participants in both groups wore 2 continuous glucose monitoring sensors provided by Medtronic for the 72 hour study period. This data serves as a **secondary endpoint** with the statistics of **average sensor BG**, **standard deviation in sensor blood glucose** and hyperglycemic markers of **AUC in hyperglycemia** (BG >140 mg/dL) and **percent time in hyperglycemia** (BG>140 mg/dL) and the hypoglycemic markers of **AUC in hypoglycemia** (<70 mg/dL) and **percent time in hypoglycemia** (BG<70 mg/dL).

Two Hour Mixed Meal Tolerance Test (MMTT): This protocol has been validated as a sensitive indicator of endogenous insulin production [72]. **Glucose** and **C-peptide** were drawn at baseline and every hour for 2 hrs. The patients were given Boost HP 6 cc/kg (max 360 ml), ingested within 5 min, after the time 0 blood draw. This test was performed at the pre-transplant visit and at the 6 month follow-up visit as part of the patient's routine transplant care.

Insulin Use: Total daily insulin requirements were calculated as **average total daily dose (TDD) of insulin** (U/day) and TDD per unit body weight (U/kg/day) over the 72 hour investigational period. Current insulin requirements were also reviewed at the 6 month follow up visit as TDD and TDD per kg.

Hemoglobin A1c Values (A1c): A measure of average serum blood glucose over the previous 3 months, hemoglobin A1c measurement has become standard of care for monitoring diabetes control and compliance with therapy. It has recently been added to the diagnostic criteria for diabetes. It was measured at the pre-transplant visit to validate that the participant did not have pre-existing diabetes. Hemoglobin A1c was also measured at the 6 month follow-up visit as part of the patient's routine post-transplant care, and was used to compare the glycemic status of the study and conventional therapy groups.

C-Peptide Values: C-peptide is an inert polypeptide which is cleaved from insulin as part of endogenous insulin production, but which is lacking in commercially produced insulin. It is used as a marker of endogenous insulin production. In TPIAT patients C-peptide levels correlate with successful graft function. C-Peptide levels were obtained an all study participants at the pre-transplant visit (as part of the MMTT), daily during the 72 hour intervention period, at the 14 and 28 days post-transplant visits, and at the 6 month follow-up visit (as part of the MMTT).

2.6 Total Pancreatectomy and Islet Auto-Transplantation Procedure

All participants underwent Total Pancreatectomy consisting of partial duodenectomy, Roux-en-Y duodenojejunostomy, choledochojejunostomy, and splenectomy as described in previous surgical literature from UMN [19-21] (Figure 1.A.). Isolation and purification of the patient's own islet cells was performed in the University of Minnesota Molecular and Cellular Therapeutics GMP Facility. Using a pressure-controlled pump system, the pancreas was distended with cold enzyme solution [73]. The pancreas was then digested using the semi-automated method described by Ricordi [74]. The islets were then infused into a tributary of the portal vein, or if elevated portal pressures prevented infusion of all the islets intraportally, the remaining islets were transplanted into the peritoneal cavity (Figure 1.B).

Immediately after surgery all patients were started on a continuous intravenous (IV) insulin infusion protocol (IIP) with the goal of maintaining BG in the range of 80-125 mg/dL. This protocol is similar to the pediatric IIP recently published by our group [20]. The protocol is an electronic medical record-based protocol which addresses the recommended IIP elements of: frequent BG checks, use of current as well as previous BG values in determining insulin rate adjustments, use of rate of change in BG level in determining insulin rate adjustments, protocolized nurse-directed decisions, and minimizing hypoglycemia. As with all TPIAT patients, participants in this study were kept on the IIP from the completion of surgery until they reached goal J-tube feeds.

After surgery all patients were started on trophic J-tube feeding on post-op day 1. Trophic feeding is generally started at a rate of 10 mL/hr with an adult liquid formula such as Impact Peptide 1.5 Cal/mL or Peptamen 1.5 Cal/mL as advised by the Registered Dietitian and determined by Transplant Surgery service. Feeds were then gradually advanced to the goal rate advised by the Registered Dietician and as tolerated by the patient with final decision making resting with the Transplant Surgery team; a process which generally takes 4-8 days. Once

patients were determined to be stable on their goal feeding rate, they were transitioned to SQ insulin therapy per their random group assignments for the 72 hour investigational period. Patients were kept on continuous J-tube feeding at their goal rate throughout the study period. Patients did not have any PO intake through the end of the study period.

2.7 Subcutaneous Insulin Investigational Period

Participants randomized to the control arm (Multiple Daily Injection insulin therapy) received SQ insulin therapy per standard post-TPIAT protocol as directed by the primary endocrinology team, without influence or input by the research team. Insulin dose determination and adjustments were made by the adult endocrinologist, endocrinology fellow, or diabetes ARNP, as would generally be done had the patient not participated in the study. Participants in the control group received long-acting insulin, either glargine (Lantus) or detemir (Levemir), calculated based on the total daily IV insulin rate at stable enteral feeds, split into one or two doses a day. BG was monitored every 4 hours by bedside glucometer and rapid-acting insulin aspart (Novolog) was given as a correction every 4 hours as needed for BG levels > 125 mg/dL with sensitivity determined by patient's daily insulin requirements. The long-acting insulin dose was adjusted as needed based on daily correction requirements. During this time period, trained study staff obtained q4h YSI reference BG values and daily AM C-peptide and BG values. Participants also wore 2 CGM devices (1 primary and 1 backup). These devices did not provide real-time data and the results were reviewed only after the 72 investigational period for comparison with the experimental group.

Participants randomized to the experimental arm received SQ insulin as directed by the Medtronic ePID 2.0 Control Tool system. Participants in this group wore a Medtronic Paradigm REAL-Time Insulin pump loaded with insulin aspart (Novolog) as well as two Enlite Glucose Sensors attached to MiniLink REAL-Time Transmitters (Figure 3. and Table 4.).

Figure 3. Medtronic ePID 2.0 System Patient Diagram (I.) and Concept Diagram (II.). Letters correspond to component descriptions in Table 4.

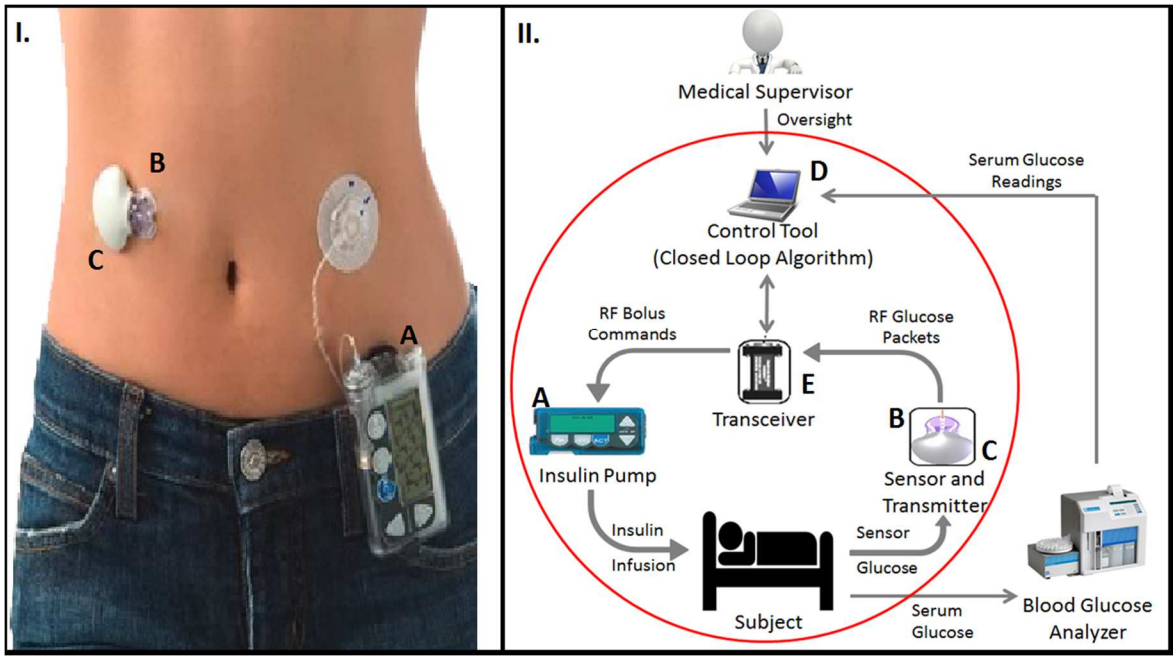


Table 4. Devices used in the ePID 2.0 System. Letters correspond to components in Figure 3.

	Generic Name	Device Name	Model Number	Device Description	Approval Status
A	Insulin Pump	Medtronic Paradigm REAL-Time Insulin Pump	MMT-722	Ambulatory, battery operated, rate-programmable infusion pump designed to deliver insulin from a reservoir. The reservoir is driven by a motor.	Commercially available
B	Subcutaneous glucose sensor	Enlite Glucose Sensor	MMT-7008X	Single-use, disposable sensor designed to continuously monitor interstitial glucose concentrations for up to 6 days. It is inserted into the subcutaneous tissue of the user and connected to a transmitter device.	Commercially available
C	Transmitter	MiniLink REAL-Time Transmitter (modified to transmit every minute)	MMT-7703XNA	Provides power to the sensor and measures the sensor signal current that is converted to a digital signal, and is filtered to reduce noise artifact. The digital signal is then transmitted to a receiving device (Medtronic Paradigm insulin pump) via radio frequency (RF) once every 1 minute.	Investigational
D	Control Tool software	Control Tool Software, version 5.1 that is housed on a laptop	NA	The control tool software houses the Closed Loop algorithm that calculates an insulin dose based on information received from the insulin pump and/or transmitter	Investigational
E	Signal Transceiver	ComLink	MMT-7304NA	Sends messages from the Control Tool software to the pump and sends messages from the pump or transmitter to the Control Tool software	Commercially available

The participants stable total daily dose of IV insulin and IV insulin rate were used by the custom made Medtronic TPIAT Gains Calculator to determine the parameters for initial controller settings (Table 5.).

Table 5. Default Parameter Settings and ranges for the ePID 2.0 System

Parameter	Nominal Value	Lower Bound	Upper Bound
Controller gain: K_p	$K_{p_0} = \frac{I_{TDD} * 60}{90 * 1500}$	$0.5 * K_{p_0}$	$1.2 * K_{p_0} * (1 + \frac{1}{6}(\gamma_1 + \gamma_2 + \gamma_3))$
Integral time constant: T_I	250	100	750
Derivative time constant: T_D	50	40 (normal) 0 (hypoglycemia)	100
I_{SC} feedback gain: γ_1	0.64935	0	6.0
I_P feedback gain: γ_2	0.34128	0	6.0
I_{EFF} feedback gain: γ_3	0.0093667	0	6.0
Target glucose (set point): T_{BG}	100-110	90	120.0

- I_{TDD} is the total daily insulin dose (U/day). The controller gain varies based on the total amount of exogenous insulin required by the individual patient. Subtle fluctuation in BG requiring frequent adjustment in the basal delivery of insulin is achieved by adjusting the derivative time constant (T_D) and the integral time constant (T_I) to suite glycemic control during the continuous J-tube feeding period.

During the 72 hour investigational period participants in the experimental group had their SQ insulin infusion rate adjusted every minute based on the control tool algorithm. YSI BG values were obtained q30 minutes or more frequently as required by the safety protocol. Insulin rate, CGM BG values and YSI BG values were presented in real-time on the Control Tool software for review by trained study staff. Participants in this group also had reference q4h YSI BG values collected for comparison with the control group. In addition, these participants also had AM C-peptide and BG values collected. At the end of the investigational period, CGM data was extracted from the Control Tool for analysis.

2.8 CGM Analysis

This study marked the first clinical trial using the Medtronic Enlite 2 subcutaneous glucose sensors as part of a closed loop system. It was also one of the first studies to use CGM in a post-surgical patient population and in patients with some level of endogenous islet function.

Transient abdominal and peripheral edema was anecdotally observed by the researchers during the pilot study with possible low signal strength as a result. The study protocol called for sensor recalibration for 2 values in a row with an absolute relative difference (ARD) of ≥20% or one value with an ARD of ≥ 30%. Device recalibration and switching of the active sensor was also permissible at the investigator's subjective discretion. To evaluate CGM performance in this pilot study a *post hoc* analysis of was conducted of CGM bias, mean absolute relative difference (MARD), calibration values, recalibration frequency, active sensor changes, and Clarke Error Grid analysis[75, 76].

2.9 Data Analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at UMN [77]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. All analyses were performed using SAS version 9.3 (Cary, NC).

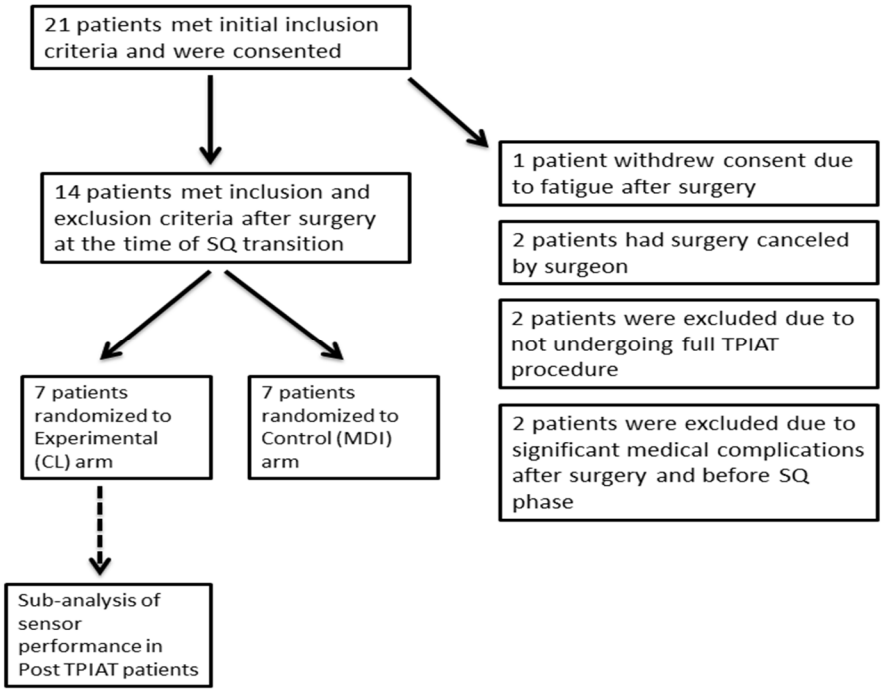
Data are presented as mean ± standard deviation or as percentage (95% confidence interval), except where otherwise noted. Hypothesis testing was conducted using two-sided Student's t-test with equal variance. Values of $p \leq 0.05$ were considered statistically significant. AUC for CGM analysis of experimental and control patients was determined via Riemann sums method with width of 5 and 1 minutes, respectively. Analysis for confounding and effect modification was conducted using multiple least-squares linear regression. Clarke Error grid analysis was conducted using standard regional bounds defined by Clarke et al [75, 76].

3.0 RESULTS

3.1 Patient Population, Demographics and Pre-Transplant History

In total 21 patients who met initial recruitment criteria and were consented for possible study participation (Figure 4.). Of these, 7 patients were not subsequently started on study protocol due to canceled surgery in 2 patients, only partial completion of surgical procedure in 2 patients, post-surgery complications in 2 patients and withdrawal of consent in 1 patient. Of the patients who met inclusion and exclusion criteria at the time of SQ transition 7 patients were randomized to the experimental arm and 7 were randomized to the control arm.

Figure 4. Study Recruitment, Enrollment and Randomization



Within the entire study cohort there were 5 men and 9 women with an average age of 35.9±11.4 years-old. Demographic characteristics of age, weight at transplant, and BMI at transplant were not significantly different between the two study groups (Table 6.). Primary

etiology of CP was roughly evenly distributed between the two groups. Pre-transplant values of hemoglobin A1c, fasting BG, fasting C-peptide, and peak MMTT C-peptide were also not significantly different between groups. The islet yield transplanted was quite high overall (5432±2983 IEq/kg) and was not significantly different between the two study groups. The time between surgery and SQ transition (Days on drip) was significantly shorter for the experimental group than for the control group (5.1±1.1 days v. 6.9±1.1 days; p=0.011). These surgical factors (Islet Yield and Days on Drip) will be more thoroughly explored in the following sections.

Table 6. Demographic and Baseline Patient Characteristics (* indicates statistical significance with p < 0.05)

	Control Group	Experimental Group	p-value	
Age (yrs)	33.1 ± 13.3	38.6 ± 9.4	0.394	
Sex M/F (% male)	4/3 (57%)	1/6 (14%)		
Wt at Tx (kg)	76.7 ± 23.7	66.1 ± 10.3	0.298	
BMI at Tx (kg/m2)	24.9 ± 5.7	25.3 ± 4.5	0.899	
Hemoglobin A1c (%)	5.4 ± 0.5	5.1 ± 0.2	0.132	
Fasting BG (mg/dL)	95 ± 13	89 ± 6	0.308	
Fasting C-peptide (ng/mL)	3.0 ± 3.7	2.0 ± 0.6	0.543	
Peak MMTT C-peptide (ng/mL)	5.8 ± 4.4	6.4 ± 2.2	0.740	
Islet Yield (IEq/kg)	4245 ± 2174	6619 ± 3357	0.142	
Days on drip (days)	6.9 ± 1.1	5.1 ± 1.1	0.011	*
Primary Etiology of CP				
Identified Genetic Mutation (PRSS1, SPINK1, CFTR)	1 (14%)	3 (43%)		
Mechanical Dysfunction (Pancreatic Divisum, Sphincter of Oddi Dysfunction, Annular Pancreas)	4 (57%)	3 (43%)		
Idiopathic Pancreatitis	2 (29%)	1 (14%)		

3.2 Subcutaneous Insulin Therapy 72 Hour Investigational Period

The results from the 72 hour investigational period (Table 7.) support *Hypothesis 1* by showing that the average serum BG was significantly lower in the experimental group than in the control group (111±4 mg/dL v. 130±13 mg/dL; p=0.003). In fact, the highest experimental group patient's average BG was lower than the lowest control group patient's average BG (Figure

5).

The standard deviation for the experimental group was lower than that for the control group (14.1±3.3 mg/dL v. 21.0±10.2 mg/dL; p=0.115), though with a p-value > 0.05. This demonstrates a trend in support of *Hypothesis 2* within this pilot study, showing that the effect was possibly underpowered but in the hypothesized direction.

Table 7. Group Comparison for 72h Investigational Period (* indicates statistical significance with p < 0.05)

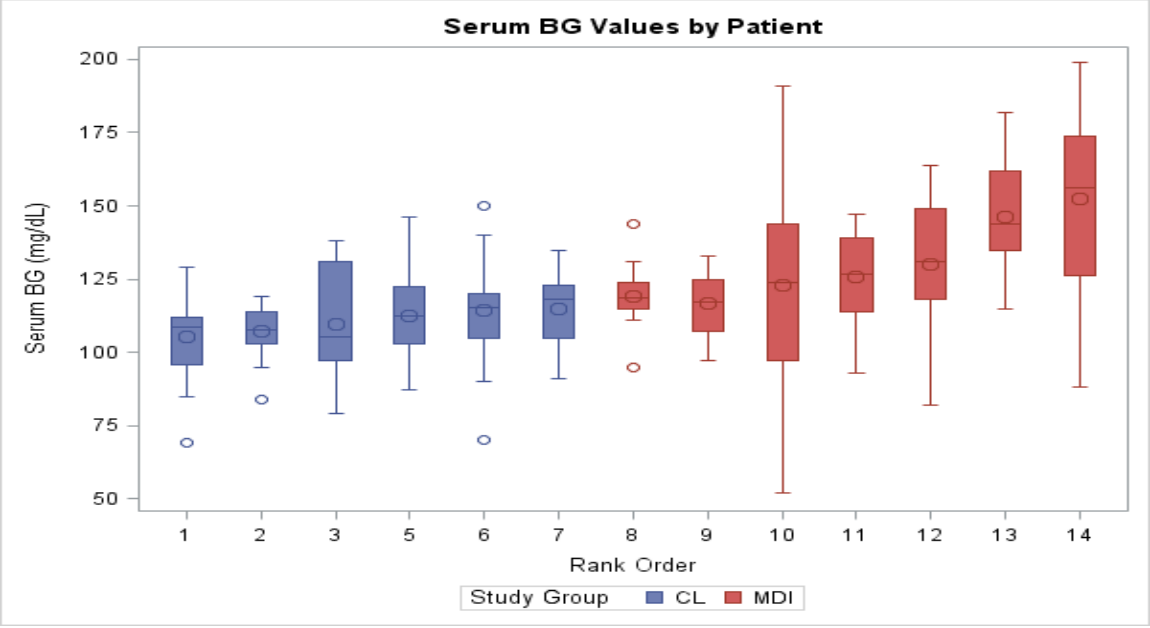
	Control Group	Experimental Group	p-Value	
Serum BG Avg (mg/dL)	130 ± 13	111 ± 4	0.003	*
Serum BG StDev (mg/dL)	21.0 ± 10.2	14.1 ± 3.3	0.115	
Sensor BG Avg (mg/dL)	125 ± 20	114 ± 4	0.193	
Sensor BG StDev (mg/dL)	21.0 ± 10.3	20.1 ± 5.1	0.848	
% in Range 70-140 mg/dL (%)	70.6 (48.0, 93.1)	89.2 (83.5, 94.8)	0.074	
Hypoglycemia				
AUC < 70 mg/dL (min*mg/dL/day)	1615 ± 4267	146 ± 270	0.381	
% < 70 mg/dL (%)	4.8 (-6.9, 16.6)	1.1 (-0.3, 2.6)	0.461	
Hyperglycemia				
AUC > 140 mg/dL (min*mg/dL/day)	7860 ± 11444	2025 ± 1177	0.205	
% > 140 mg/dL (%)	23.7 (1.5, 46.0)	9.7 (4.9, 14.5)	0.157	
AM C-Peptide Avg (ng/mL)	1.6 ± 1.0	1.3 ± 0.6	0.443	
TDD of Insulin (U/kg/day)	0.56 ± 0.31	0.26 ± 0.17	0.040	*

The Area Under the Curve analysis showed lower values for the experimental group than for the control group for both hypoglycemia (146±270 min*mg/dL/day v. 1615±4267 min*mg/dL/day; p=0.381) and hyperglycemia (2025±1177 min*mg/dL/day v. 7860±11444 min*mg/dL/day; p=0.205). While neither of these measures met the criteria for statistical significance, within this pilot study the trend was in the hypothesized direction. The percent time in both hypoglycemia and hyperglycemia, also followed this trend. These findings provide support for *Hypothesis 3* that there appears to be less time spent in hyperglycemia and

hypoglycemia for the experimental group than for the control group. Further support for this hypothesis comes from the fact that the experimental group was in the target range of 70-140 mg/dL 89.2 % (83.5, 94.8) of the time and the control group was in range 70.6% (48.0, 93.1) of the time, a very clinically significant difference which was just outside the range of statistical significance for this study (p=0.074). The findings also show that there is no evidence of significantly increased hypoglycemia in the experimental group than in the control group, an important safety consideration with more aggressive BG control.

There was no difference in AM C-peptide levels between the 2 groups during this study period. The total daily insulin dose in the experimental group was significantly lower than in the control group (0.26±0.17 v. 0.56±0.31; p=0.040). This is at least partially expected as it is often observed clinically that patients require 20% less insulin when delivery is continuous rather than intermittent.

Figure 5. Serum Blood Glucose Values by Patient and Study Group. Large circle denotes mean, box denotes 25th percentile, median and 75th percentile and small circles denote outliers.



3.3 Analysis for Confounders and Effect Modifiers

For the four *a priori* defined hypothesis testing endpoints of average serum BG, standard deviation of serum BG, AUC in hypoglycemia and AUC in hyperglycemia additional analysis was conducted to investigate for possible confounding or effect modification (Appendix 7.3).

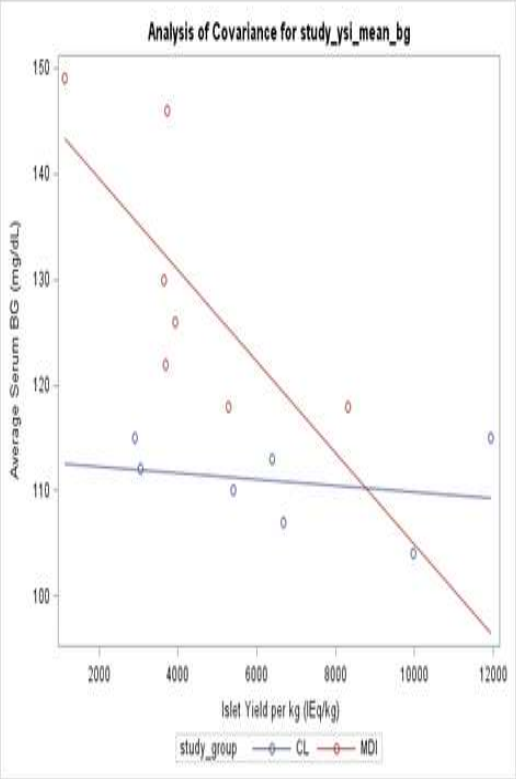
As noted above, the average days on insulin drip, or days between surgery and beginning of the SQ insulin period, was significantly different between the two groups. This raised concern for the possibility of this factor as a potential confounder for the differences observed between the 2 groups. Multiple least-squares regression analyses were conducted to look at the relationship between days on drip and study group effects on the 4 primary endpoints. The data gave no sign that there is any effect of days on drip on the study group effects seen for these endpoints.

Due to their role in insulin secretion and BG regulation we hypothesized that the number of islets transplanted may be an effect modifier for all aspects of glucose regulation (Appendix 8.3 and Figure 6.). Islet yield was thus investigated using multiple least-squares regression analysis looking at the relationship between islet yield (IEq/kg) and study group effects on the 4 primary endpoints. Islet yield was a significant predictor of average serum BG ($p=0.0188$), standard deviation in serum BG ($p=0.0340$), and AUC in hyperglycemia ($p=0.0164$). No effect was observed for AUC in hypoglycemia ($p=0.8060$). Statistically significant interaction was observed for average serum BG ($p=0.0348$) and AUC in hyperglycemia ($p=0.0145$), and substantial interaction was observed for standard deviation of serum BG ($p=0.0842$).

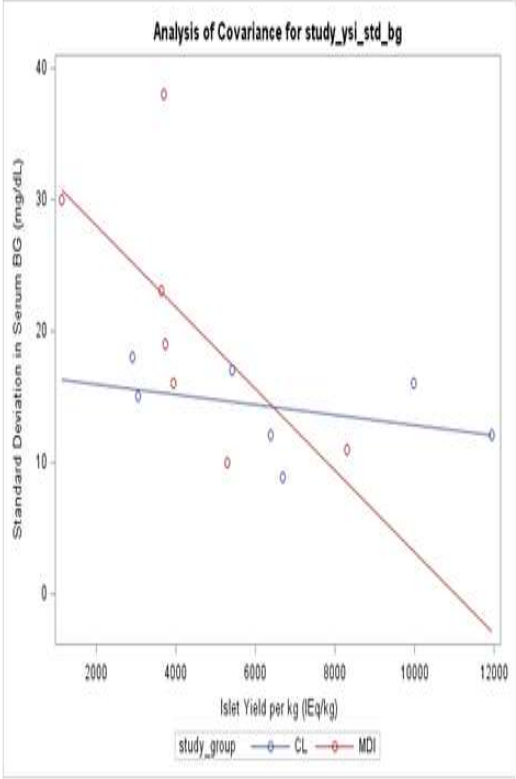
More thorough analysis of the covariance plots reveals an apparent trend that islet yield had minimal effect on the experimental group but a marked effect on the control group with higher islet yield being correlated with lower average serum BG, standard deviation in serum BG and AUC in hyperglycemia. While this pilot study was not intended to investigate this effect modifier, these observed effects warrant significant discussion as well as consideration in planning future phases of this research.

Figure 6. Multiple Least-Squares Linear Regression Analysis for Effect Modification

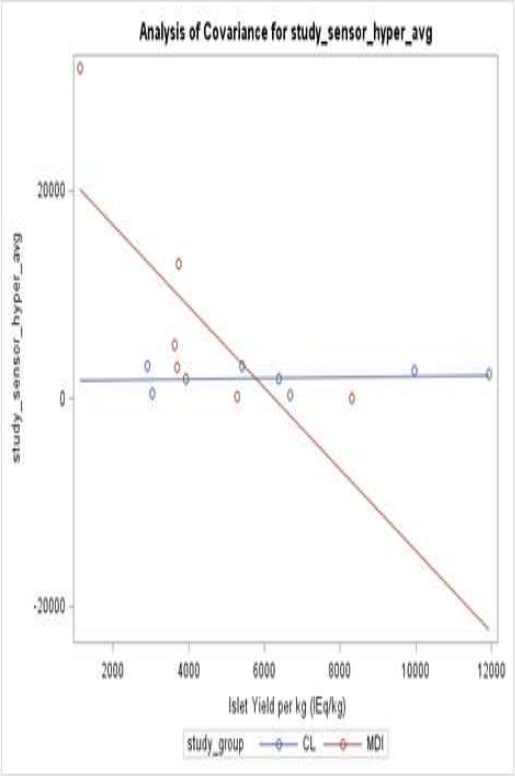
Multiple Least-Squares Linear Regression Analysis of Islet Yield and Study Group on Average Serum BG



Multiple Least-Squares Linear Regression Analysis of Islet Yield and Study Group on Standard Deviation of Serum BG



Multiple Least-Squares Linear Regression Analysis of Islet Yield and Study Group on AUC in Hyperglycemia



3.4 Follow Up Visit Data

To date, all 14 participants have returned for 14 and 28 days post-surgery follow up for random BG and C-peptide testing. No significant differences were observed between the two treatment groups for either random BG or C-peptide at 14 or 28 days post-surgery (Table 8.).

Table 8. Follow Up Visit Data

	Control Group	Experimental Group	p-Value
Day 14 Post-TPIAT (n=14)			
BG (mg/dL)	135 ± 81	108 ± 16	0.4012
C-peptide (ng/mL)	1.0 ± 0.9	1.6 ± 0.9	0.2208
Day 28 Post-TPIAT (n=14)			
BG (mg/dL)	113 ± 29	100 ± 21	0.3258
C-Peptide (ng/mL)	1.0 ± 1.2	1.7 ± 1.2	0.3116
6 Months Post-TPIAT (n=5)			
Hemoglobin A1c (%)	6.0 ± 0.1	6.0 ± 0.2	0.7663
TDD of Insulin (U/day)	7.0 ± 5.6	5.4 ± 0.7	0.6438
Fasting BG (mg/dL)	94 ± 1	90 ± 4	0.3339
Fasting C-Peptide (ng/mL)	0.8 ± 0.6	1.3 ± 0.8	0.4579
Peak C-Peptide (ng/mL)	3.8 ± 2.1	4.0 ± 3.3	0.9506

The second aim of this study was to assess islet function at 6 months post-surgery. To date, only 5 patients (3 experimental and 2 control) have reached the 6 month follow-up time point. Interim analyses of the 6 month follow up endpoints do not reveal any significant differences between the two treatment groups. Full assessment of *hypothesis 4* is considered incomplete at this time as only 5 of 14 study participants (35.7%) have yet reached this follow up time point.

3.5 Safety Analysis

Due to the use of investigational medical technology in a research setting, this project required an extensive safety protocol (Appendix 7.1) and adverse event reporting guidelines (Appendix 7.2). No participants in either group experienced a severe adverse event of grade 3 or greater. No participants in either group required withdrawal from the investigational protocol for safety concerns. One participant in the control group experienced a grade 2 event of seizure without hypoglycemia. This was determined by the primary team to be a reaction to narcotic medications used for post-surgery pain control. One participant in the control group experienced 2 episodes of symptomatic hypoglycemia with BG values in the 50-60 mg/dL range and resolving with IV dextrose. Two participants in the experimental group each experienced one episode of asymptomatic hypoglycemia documented in the 50-60 mg/dL range, resolved with IV dextrose; in review, both events appear to be related to incorrect device calibration. A third patient received IV dextrose for a suspected hypoglycemic event (BG measured 50-60 mg/dL range) but was subsequently found to have diluted serum samples and in retrospective review this event was attributed to factious hypoglycemia.

The FDA required testing of serum ketone levels for all experimental patients at the end of the study period to ensure that no patients were in diabetic ketoacidosis at the end of the study. All patients had normal ketone levels (< 0.6 mmol/L) with only 2 of 7 having undetectable ketone levels and the overall average being 0.21±0.19 mmol/L.

3.6 CGM Analysis

Sub-analysis of sensor performance of the Enlite 2 sensors in the 7 experimental patients was conducted correlating q30 minute reference YSI BG values with calibrated sensor readings

10 minutes later to construct a Clarke Error Grid (Figure 7. and Table 9.). This analysis produced 990 paired YSI-Sensor sets over 7 individual patients totaling 21 days of observations. With regards to the Clarke Error analysis, sensor performance had 86.1% of all pairs in Zone A and 99.4% of all pars in Zones A or B.

Figure 7. Clarke Error Grid of CGM Function

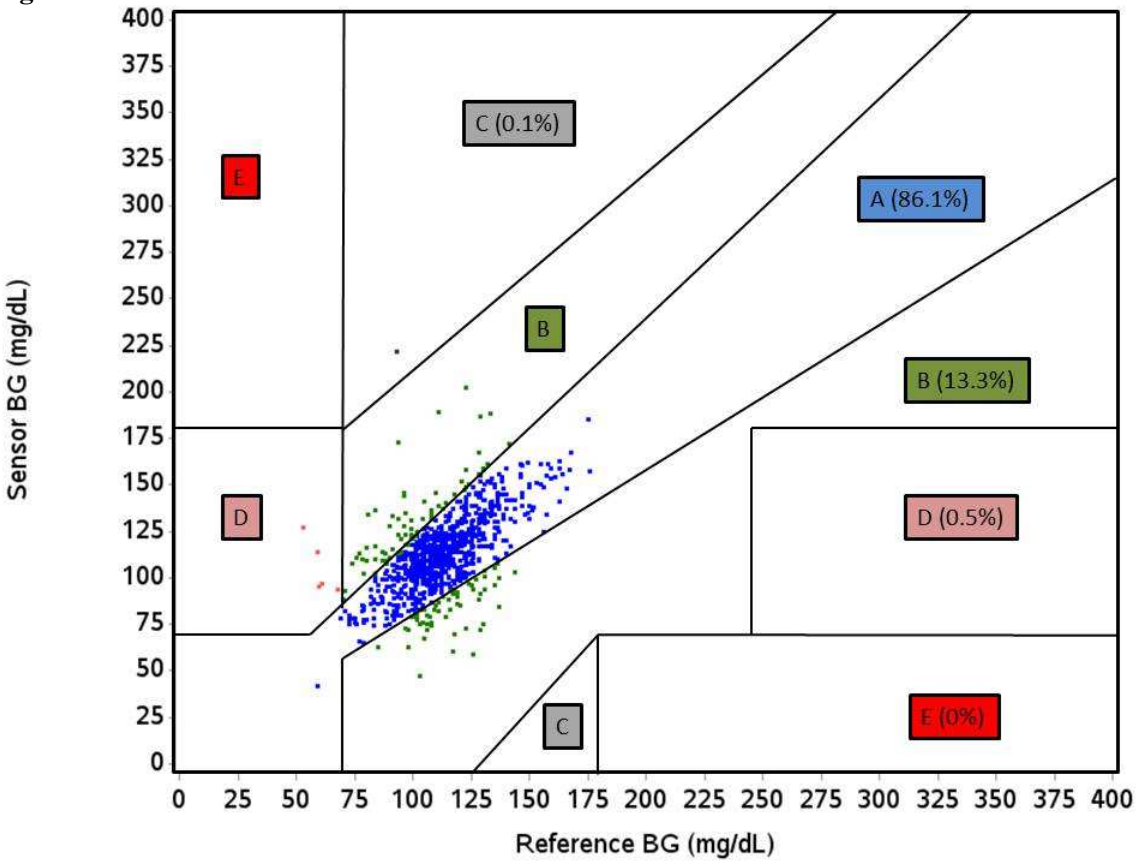


Table 9. Clarke Error Grid Analysis

	Region					
EGA Metrics	**A**	**B**	**C**	**D**	**E**	**Total**
Points	852	132	1	5	0	990
%	86.1	13.3	0.1	0.5	0.0	100.0
% A+B	99.4					

Overall sensor analysis showed MARD of 11.0±11.5%, with substantial variability across different patients (Table 10). Excluding the first 12 hours after sensor placement, the sensors were recalibrated an average of 8.3 times per day and the active sensor was switched an average of 1.4 times per day (Table 11.). Average calibration factor across all patients was 7.692±3.786 mg/nA*dL with an acceptable range being 1.5 to 20 mg/nA*dL.

Table 10. Continuous Glucose Monitor Bias and Mean Absolute Relative Difference

	Bias (mg/dL)		ARD (%)	
Patient	**Mean**	**StDev**	**Mean**	**StDev**
CLTPIAT01	0.6	12.6	8.83	7.81
CLTPIAT03	-3.3	17.1	10.45	10.27
CLTPIAT05	-0.5	24.3	16.59	17.16
CLTPIAT06	7.6	12.6	10.9	9.32
CLTPIAT09	-1.3	16.7	10.94	10.62
CLTPIAT11	4.7	13.7	10.18	9.09
CLTPIAT13	-0.1	13.7	9.08	16.21
OVERALL	**1.1**	**15.8**	**11.0**	**11.5**

Table 11. Continuous Glucose Monitor Calibration Data

	Cal Factor (mg/nA*dL)		Recalibrations per 24 hr#	Active Sensor Changes per 24 hr#
Patient	**Avg**	**StDev**		
CLTPIAT01	5.597	0.652	9.2	1.6
CLTPIAT03	11.115	9.923	5.6	0.4
CLTPIAT05	7.492	4.550	14.0	2.8
CLTPIAT06	9.495	2.531	7.6	0.0
CLTPIAT09	11.091	7.042	12.4	2.4
CLTPIAT11	4.500	0.886	5.6	1.6
CLTPIAT13	4.552	0.916	3.6	1.2
AVERAGE	**7.692**	**3.786**	**8.3**	**1.4**

Over the 72 hour study period excluding the initial 12 hours

4.0 DISCUSSION

In patients with chronic pancreatitis, TPIAT is performed to alleviate pain and minimize the risk of long-term diabetes. Success of islet engraftment is heavily dependent on maintenance of narrow-range euglycemia in the post-transplant period. Closed loop insulin pump systems have never previously been used in islet transplant populations but have been shown to maintain narrow-range euglycemia in patients with type 1 diabetes. This study aimed to assess the efficacy and feasibility of a CL system in patients after TPIAT. Overall the pilot results from this efficacy and feasibility study support the effectiveness and safety of CL systems to improve glycemic control in the TPIAT population in the post-transplant period.

4.1 Experimental Period Findings

The major goal of insulin therapy in the post-transplant period is to limit malglycemia during the immediate post-transplant period. Malglycemia is the combined effect of hyperglycemia, hypoglycemia, and glycemic variability and has been shown in other cell transplant populations, notably hematopoietic cell transplant (HCT) patients, to have negative effects on post-transplant outcomes [78-80].

The overall effect of CL therapy was demonstrated in this study to be successful in reducing hyperglycemia with likely reduction in glycemic variability without negatively impacting hypoglycemia (Table 7. and Figure 5.). The overall time in range of 89.2% (83.5, 94.8) for the CL group compares favorably with other studies investigating overnight or fasting populations. O'Grady and colleagues recently utilized a similar PID system overnight in 8 patients with T1DM and found 84.5% time in target range of 70-144 mg/dL [59]. Elleri and colleagues used a MPC system overnight in patients with T1DM and found 82% time in target range of 71-145 mg/dL [53].

As noted earlier, the time from surgery to SQ conversion (days on insulin drip) was

significantly shorter for the CL group than for the control group (Table 6.). This was likely attributable to the conversion process being driven by the experimental team in the CL group and by the endocrine service in the control group. The experimental team, being very confident in the CL system, was more aggressive at pushing forward with the SQ transition whereas the endocrine service wanted to see stable IV insulin infusion rates for > 24 hours prior to giving insulin injections. In our clinical practice it has been observed that BG is more difficult to control in the immediate post-operative period than farther out as stress hormone levels are higher, pain is more severe and more fluctuant and GI absorption of feeds is less stable. For these reasons, we postulate that any bias from the experimental group transitioning to SQ earlier, should bias the results towards the null hypothesis. Multiple least squares regression analysis did not reveal significant confounding from this difference as well.

The effect modification observed based on islet yield transplanted is perhaps the most striking finding of this pilot study (Figure 6.). This sub-analysis shows that for the CL group there was no improvement in BG average, BG standard deviation or AUC in hyperglycemia with increased islet yield whereas for the control group higher islet yield was associated with lower values for these 3 glycemic markers. We postulate that in the CL group more aggressive continuous insulin therapy was able to maintain near normo-glycemia allowing for significant islet cell rest and thus a lack of variation based on islet cell yield. While for the control group intermittent insulin therapy relied somewhat on endogenous insulin production from transplanted islets to handle variations in glycemia with success of this effect based on transplanted islet cell mass; thus for the control group there was suboptimal islet rest during this period.

4.2 CGM Performance

An important aspect of CL system performance is continuous glucose monitor performance. This technology has been mainly designed for outpatient use among healthy

patients with type 1 diabetes. In this study, CGMs were used in a post-surgical population. CGM devices are recommended to be worn on the abdomen with the thigh being an alternate site. Concern arose among the investigators during this pilot investigation that transient edema could be markedly effecting the CGM sensor strength and contributing to more frequent recalibrations in this population. For this reason a sub-analysis was conducted among the 7 CL patients looking at CGM performance during the 72 hour investigational period.

A traditional Clarke Error grid was constructed looking at relative agreement between calibrated sensor reading and reference YSI serum BG (Figure 7. and Table 9.). This data demonstrated that with recalibration, Enlite 2 sensor performance in this population was very good with > 85% of values in Zone A and > 99% of values in Zones A or B. Further analysis of Mean Absolute Relative Difference (MARD) between the reference and CGM values revealed relatively strong correlation at 11.0% MARD overall (Table 10.).

The other aspect to consider though is what level of supervisory rigor was required to achieve this level of system correlation. Medtronic recommends a calibration factor for the Enlite 2 in this system between 1.5 and 20 mg/nA*dL and recommends recalibration for 2 values in a row with an ARD of ≥20% or one value with an ARD of ≥ 30%. To more closely replicate true clinical utility, sensors were placed in this study just prior to SQ transition rather than a day in advance, as is done in many other studies. Sensors were frequently recalibrated during the first 12 hours, considered the initial "settling time" for the sensor. After the first 12 hours, sensors in this study were recalibrated an average of 8.3 times per day or roughly once every 3 hours, including overnight (Table 11.). Furthermore the active sensor was switched 1.4 times per day. This level of rigor achieved a very good calibration factor of 7.692 mg/nA*dL across the entire investigational period. It should be noted that this analysis is a *post hoc* investigation of pilot data and no protocols were in place during the study to minimize recalibrations or active sensor changes.

Only within the past 1-2 years have publications been coming out which investigate the role of CGM technology in post-surgical populations, most often cardiac surgery patients. A recent study from Siegelarr and colleagues investigated CGM use after cardiac surgery [81]. They found MARD values of 11% and 14% for the Navigator and Guardian sensors investigated. They placed sensors on the abdomen the day before surgery and calibrated devices "according to the manufacturers' instructions." No information on calibration factors was provided. Saur and colleagues also investigated CGM after cardiac surgery using the Symphony CGM system and found 99.6% of readings in Zones A and B with a MARD of 12.3% [82]. They calibrated the sensors every 4 hours. Schuster and colleagues have also recently published an analysis of CGM data in a broader SICU population and found a MARD of 15.9% with 71.3% of values in Zone A and 98.9% of values in Zones A and B [83]. Their study used only 3 calibrations per day. Overall, the findings from this study reveal similar MARD and Zone A and B percentages though with somewhat higher calibration frequency than other recent studies.

4.3 Follow Up Data

Analysis of the 14 and 28 day post-surgical follow up data did not reveal any significant differences between the two groups. The 6 month follow up data is only partially collected and will not be complete until after initial publication of this study's results. We consider it unlikely that only 3 days of improved glycemic control, though both clinically and statistically significant in magnitude, would produce observable improvements in long term islet function or insulin requirements. While such a study has never been conducted previously in islet transplant patients, this hypothesis is based on the limited findings from the Buckingham "metabolic study" which did not show improved beta-cell survival with intensive CL therapy shortly after diagnosis of type 1 diabetes [84].

4.4 Comments on Efficacy and Feasibility

Overall the CL system was very effective in controlling BG in a narrow range after TPIAT. This system produced lower average BG with increased percent time in range without increasing hypoglycemia when compared to conventional MDI therapy. At this stage of device development clinical feasibility was significantly limited by the supervisory requirement for q30 min serum BG sampling for the CL patients as well as the need for constant device supervision by a trained medical provider. The frequency of sensor recalibration at every 3-4 hours also limits overall clinical feasibility at this time. The CL system was also found to be safe overall with no SAE's in either group. There were no episodes of symptomatic hypoglycemia in the CL group and the overall frequency of hypoglycemia requiring intervention was less than once per day in both study groups.

Since the initial design and implementation of this study, CL technology has continued to move forward with more recent experimental systems having the control algorithm housed on the insulin pump thereby removing an additional variable with potential for communication error. In addition, next generation CGM sensors are advertised as being more stable and requiring fewer recalibrations. The transmitters for these sensors will also communicate with low energy Bluetooth rather than RF signals, further reducing missed communication errors.

4.5 Study Limitations

This study was conducted in adult patients receiving TPIAT at the University of Minnesota. The findings from this pilot study may have limited generalizability to other post-surgical populations or other transplant populations. The overall islet mass transplanted in both study groups was relatively high (5432±2983 IEq/kg) and this may limit conclusions about glycemic control as it pertains to patients receiving lower islet yields. The total number of patients in this study (14 overall with 7 in each group) compares favorably with other initial

device studies (Table 2.), though a larger sample size would likely improve the significance and generalizability of the findings. The investigational period (72 hours at 6.0±1.4 days post-surgery) was relatively short and is unlikely to produce long term islet survival differences between the two groups. The time between surgery and SQ transition was significantly shorter in the experimental group than the control group, though statistical investigation of this difference did not reveal significant bias.

4.6 Future Directions of This Work

This project was a successful pilot study of a CL system in adults after TPIAT showing improved glycemic control without increased hypoglycemia or safety concerns. Now that this has been demonstrated future work involves testing a CL system in pediatric patients after TPIAT. Future projects will also involve use of a subsequent generation of this system for a longer duration of therapy including an outpatient setting. We will also continue to follow this investigational cohort of 14 patients at 6 months and likely 1 and 2 years post-surgery to look at rates of insulin independence between the two groups.

5.0 CONCLUSIONS

CL insulin systems are a valuable emerging tool for narrow range glycemic control in patients requiring insulin therapy. This technology was shown in this study to provide statistically and clinically significant improvements in glycemic parameters in adults after total pancreatectomy with islet auto-transplantation without producing associated hypoglycemia or adverse events. Continued improvements in these experimental systems, notably in CGM devices, will be essential towards moving this technology from experimentally effective to clinically feasible. This technology has the ability to provide essential islet cell rest after transplantation and may play a role in long term islet survival.

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7.0 Appendix

7.1 Safety Monitoring Plan:

Safety Monitoring Plan:

To ensure patient safety, patients on the experimental CL device will have blood glucose checked by reference method of YSI device every 30 minutes (±15 min) throughout the entire 72 hour experimental period. In addition, reference BG checks will occur under the following situations when hypoglycemia or hyperglycemia is suspected:

A. Hypoglycemia

1. If YSI glucose value falls below 80 mg/dL at any time:
    a) If YSI is 61-80 and BG was declining at <1 mg/dL/min in the previous 30 min, YSI will be checked every 15 minutes until YSI > 80. If glucose was declining at a rate >1 mg/dL/min in the previous 30 min, check YSI glucose every 5 minutes until YSI > 80.
    b) If YSI is 51-60 mg/dL, first treat hypoglycemia with oral or IV glucose. If the subject's BG was declining at <1 mg/dL/min in the previous 30 min, check YSI every 15 minutes until YSI > 80. If glucose was declining at a rate >1 mg/dL/min in the previous 30 min, check YSI glucose every 5 minutes until YSI > 80.
    c) If YSI is ≤ 50 mg/dL first treat hypoglycemia with IV glucose or glucagon. Check YSI glucose every 5 minutes until BG starts to rise, and then every 15 minutes until YSI > 80. **The study should be stopped.**
2. If subjects experience any symptoms of hypoglycemia (e.g., shakiness, dizziness, sweating, hunger, pale skin color, moodiness, clumsiness, difficulty paying attention, or tingling around the mouth). Check YSI glucose values:
    a) If YSI > 80 mg/dL, continue with protocol and check YSI glucose every 30 minutes.
    b) If YSI is 70-80 mg/dL and BG was declining at <1 mg/dL/min in the previous 30 min, YSI should be checked every 15 minutes until YSI > 80. If glucose was declining at a rate >1 mg/dL/min in the previous 30 min, check YSI glucose every 5 minutes until YSI > 80.
    c) If YSI is 51-70 mg/dL, first treat hypoglycemia with oral or IV glucose. If the subject's BG was declining at <1 mg/dL/min in the previous 30 min, YSI should be checked every 15 minutes until YSI > 80. If glucose was declining at a rate >1 mg/dL/min in the previous 30 min, check YSI glucose every 5 minutes until YSI > 80.
    d) If YSI is ≤ 50 mg/dL, first treat hypoglycemia with IV glucose or glucagon. Check YSI glucose every 5 minutes until BG starts to rise, and then every 15 minutes until YSI > 80. **The study should be stopped.**
3. If subjects display signs of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior) or severe hypoglycemic symptoms (e.g., hypoglycemic seizure, loss of consciousness, inability to properly consume treatment), first treat hypoglycemia with IV glucose or glucagon. If YSI is ≤ 80 mg/dL, check YSI glucose every 5 minutes until BG starts to rise, and then every 15 minutes until YSI > 80. **The study should be stopped.**

B. Hyperglycemia

If CGM or YSI glucose value is ≥ 250 mg/dL at any time, perform another YSI check.

a) If YSI < 250 mg/dL, proceed with investigation and re-check YSI in 30 minutes.
b) If YSI ≥ 250 mg/dL, in addition to a reference glucose check with YSI, check blood ketone levels every hour until YSI < 250 and ketones < 0.6 mmol/L.
    i. If ketones < 0.6 mmol/dL, continue the study but check the pump for occlusion and replace the infusion set if necessary.
    ii. If ketones ≥ 0.6 mmol/dL, **the study should be stopped** and the study physician will take over insulin dosing.
c) If YSI ≥ 250 mg/dL for 2 hours or ≥400 mg/dL at any time, check YSI every 30 minutes and check ketone level every hour until YSI < 250 and ketones < 0.6 mmol/L. However, **regardless of the ketone results, the study should be stopped** and the study physician will take over insulin dosing.

Study or Patient Termination

Suspension of Closed Loop System

Closed-loop control shall be suspended if the Investigator feels at any time subject safety is compromised. Replacement of the insulin pump infusion set should be performed by the Investigator along with any concurrent open-loop adjustment of insulin pump settings deemed medically necessary by the Investigator. In the unlikely event that diabetic ketoacidosis should develop, the closed-loop control shall be suspended immediately and the subject treated as medically necessary.

Patient Termination

Safety Stopping Rules:

We will stop an individual patient's study if any of the following occurs:

- The subject had a serious adverse event deemed related to study.
- Glucagon is required to treat hypoglycemia.
- The subject experiences a hypoglycemic seizure.
- The subject becomes unconscious due to hypoglycemia.
- The subject has reference BG >250 mg/dL for 2 hours or ≥400 mg/dL at any time.
- The subject has reference BG <50 mg/dL at any time.
- The subject develops emesis, nausea or abdominal pain.
- The subject develops decreased sensorium (sleepy, difficult to arouse) with or without emesis and glucose >350.
- The subject develops ketones that are confirmed at > 0.6 mmol/L at any time.
- The subject has a positive pregnancy test.
- If there is no functional CGM transmitter and receiver for >2 hours.

Study Termination

If two patients require their study to be stopped based on the above criteria, the study will be stopped.

7.2 Adverse Event Grading and Reporting

Grading of Adverse Events

The term "adverse event" (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) is any untoward medical occurrence at any dose that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Each event will be analyzed to determine is relatedness to study intervention (definitely, probably, possibly, unlikely, or unrelated) and the severity will be graded as follows, modified from the Common Toxcity Criteria:

- MILD (Grade 1) – transient or mild discomfort; no limitation in activity; no medical intervention required.
- MODERATE (Grade 2) – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required.
- SEVERE (Grade 3) – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible.
- LIFE-THREATENING or DISABLING (Grade 4) – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.
- DEATH (Grade 5) – event is a direct cause of death.

All adverse events will be graded as mild, moderate, or severe, according to the guidelines established in the current Common Terminology Criteria for Adverse Events (CTCAE).

Serious Adverse Events (SAE)

Defined as any adverse event that suggests a significant hazard, contraindication, side effect, or precaution. This includes, but may not be limited to any of the following events:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy, whether or not considered treatment-related, must be reported.
2. Life-threatening: Any adverse therapy experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death).
3. In-patient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability or incapacity.
5. Congenital anomaly/birth defect.
6. Other serious (Important medical events).

Documentation and Reporting of Adverse Events

All AEs Grade 2 and greater that occur after the subject has received investigational intervention will be documented in the CRF and will include date of onset, date of resolution (if applicable), name or brief description of the event, treatment given for the event, severity, relationship to study drug, action taken with regard to study intervention, outcome, and whether the event was classified as serious. A physician will determine the relationship of the event to the study. SAEs will be reported to Medtronic within 48 hours (24 hours if fatal or life-threatening and at least possibly related to study drug). SAE's that are at least possibly related to therapy, unexpected, and severe will be reported within 10 days to the IRB. A listing of all other adverse events will

be sent to the IRB and to Medtronic annually. All unanticipated adverse device effects will also be reported to the FDA within 10 business days after first receipt of notice of the effect. Thereafter additional reports will be provided concerning the effect as the FDA requests.

Data and Safety Monitoring Plan

For this pilot study the investigators will monitor patients throughout the 72 hour investigational period. Participants will be wearing a continuous glucose monitor which will provide continuous BG data for both closed-loop and conventional therapy patients. In addition patients on closed loop systems will have YSI BG values tested at least every 30 minutes. A research nurse will be in house with all patients on closed-loop systems and the PI or a co-investigator will be available at the hospital during weekdays and via pager on nights and weekends. Daily blood glucose values will be monitored and insulin levels adjusted for all conventional therapy patients as part of routine care. For closed-loop patients, blood glucose data will be continuously reviewed by the research nurse as part of the experimental protocol.

7.3 Analysis for Confounding and Interaction

Effect of days on drip on YSI BG Avg and test for interaction

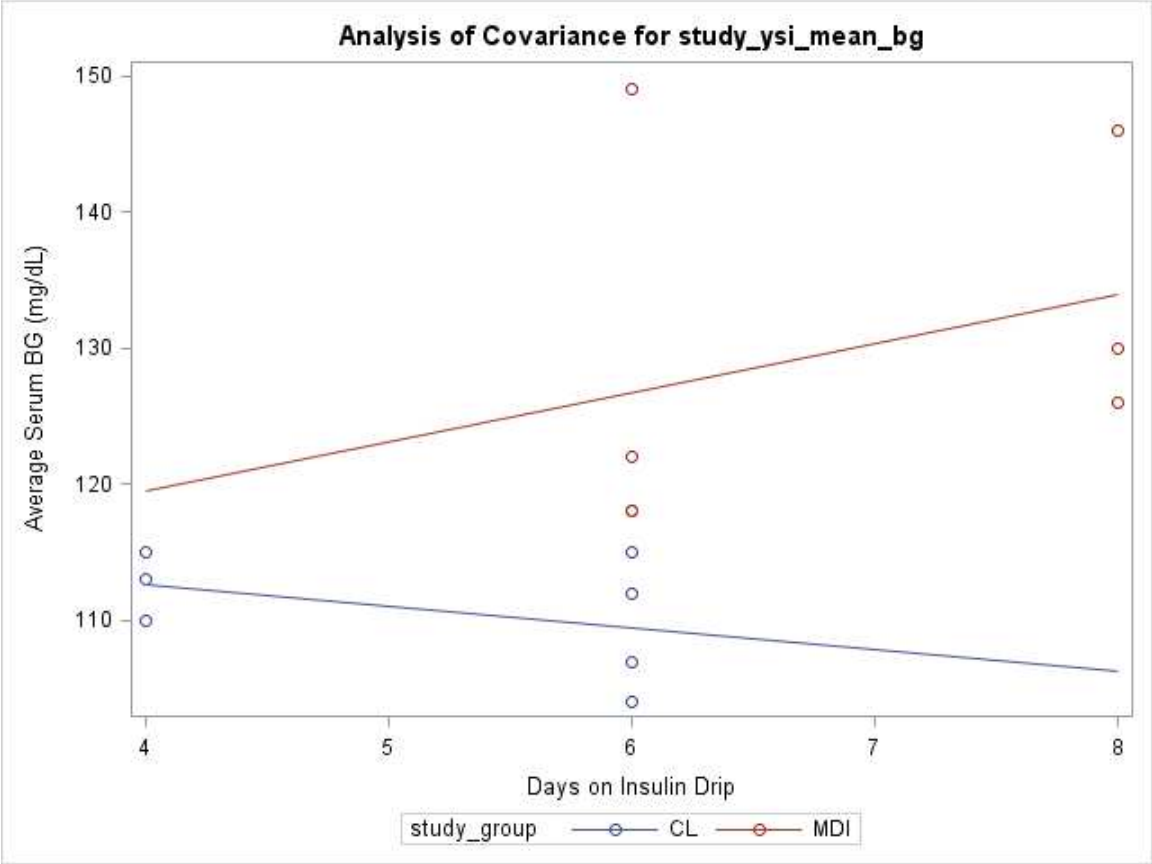
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1370.797619	456.932540	4.66	0.0275
Error	10	980.416667	98.041667		
Corrected Total	13	2351.214286			

R-Square	Coeff Var	Root MSE	study_ysi_mean_bg Mean
0.583017	8.226848	9.901599	120.3571

Source	DF	Type I SS	Mean Square	F Value	Pr > F
days_drip	1	682.6666667	682.6666667	6.96	0.0248
study_group	1	595.1250000	595.1250000	6.07	0.0335
days_drip*study_grou	1	93.0059524	93.0059524	0.95	0.3530

Source	DF	Type III SS	Mean Square	F Value	Pr > F
days_drip	1	14.29166667	14.29166667	0.15	0.7106
study_group	1	17.81818182	17.81818182	0.18	0.6789
days_drip*study_grou	1	93.00595238	93.00595238	0.95	0.3530



Effect of days on drip on YSI BG StDev and test for interaction

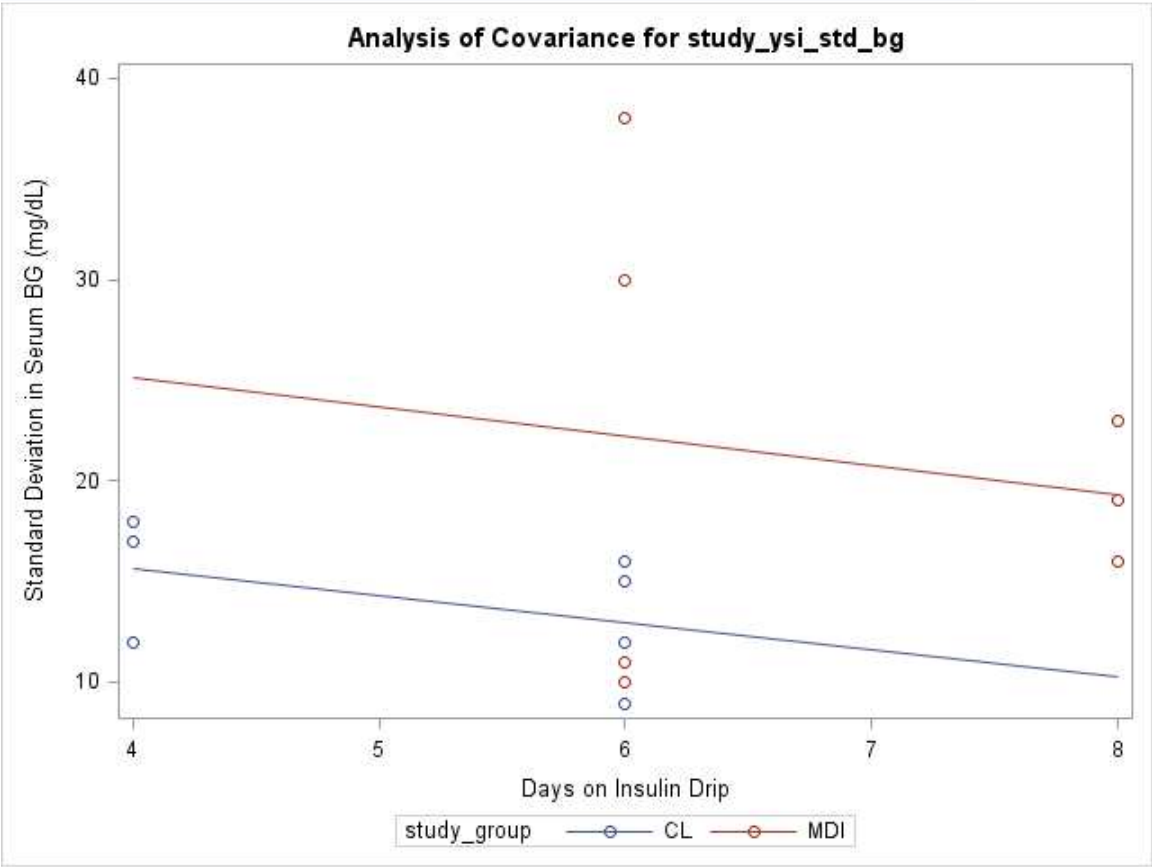
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	192.2613095	64.0871032	0.97	0.4448
Error	10	660.8908333	66.0890833		
Corrected Total	13	853.1521429			

R-Square	Coeff Var	Root MSE	study_ysi_std_bg Mean
0.225354	46.28437	8.129519	17.56429

Source	DF	Type I SS	Mean Square	F Value	Pr > F
days_drip	1	20.1666667	20.1666667	0.31	0.5928
study_group	1	172.0512500	172.0512500	2.60	0.1377
days_drip*study_grou	1	0.0433929	0.0433929	0.00	0.9801

Source	DF	Type III SS	Mean Square	F Value	Pr > F
days_drip	1	26.96005952	26.96005952	0.41	0.5374
study_group	1	9.00022727	9.00022727	0.14	0.7198
days_drip*study_grou	1	0.04339286	0.04339286	0.00	0.9801



Effect of days on drip on Hypoglycemia AUC and test for interaction

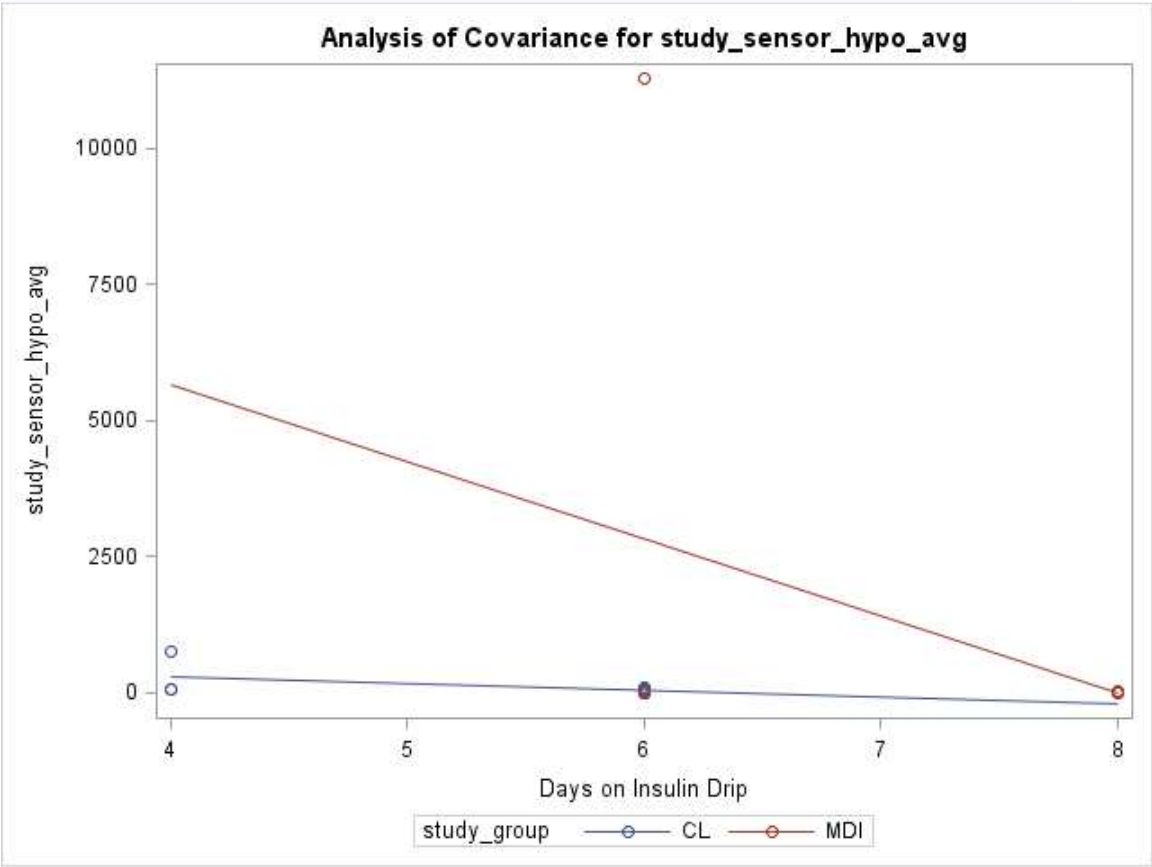
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	21275833.9	7091944.6	0.74	0.5525
Error	10	95957566.9	9595756.7		
Corrected Total	13	117233400.9			

R-Square	Coeff Var	Root MSE	study_sensor_hypo_avg Mean
0.181483	351.7641	3097.702	880.6190

Source	DF	Type I SS	Mean Square	F Value	Pr > F
days_drip	1	121742.52	121742.52	0.01	0.9125
study_group	1	15501312.00	15501312.00	1.62	0.2325
days_drip*study_grou	1	5652779.43	5652779.43	0.59	0.4605

Source	DF	Type III SS	Mean Square	F Value	Pr > F
days_drip	1	8072639.15	8072639.15	0.84	0.3806
study_group	1	10000149.09	10000149.09	1.04	0.3314
days_drip*study_grou	1	5652779.43	5652779.43	0.59	0.4605



Effect of days on drip on Hyperglycemia AUC and test for interaction

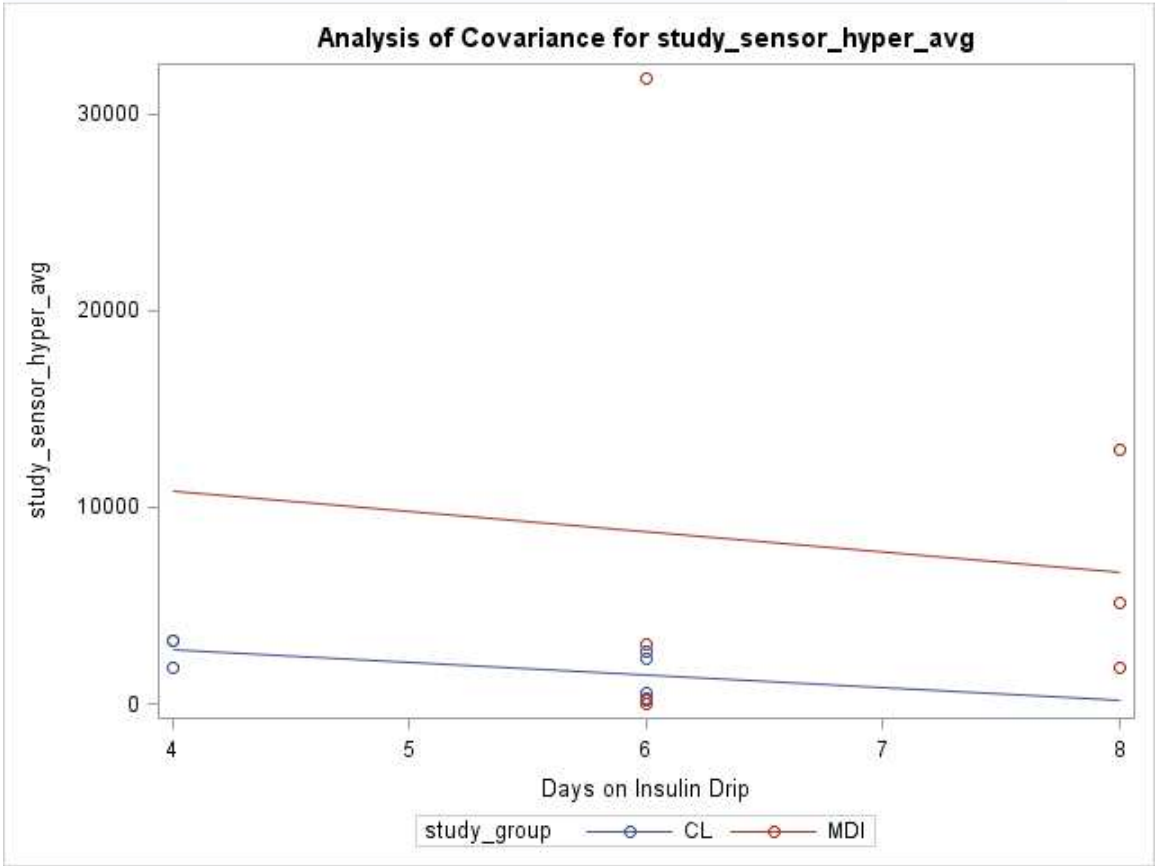
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	129457308.5	43152436.2	0.55	0.6592
Error	10	783853539.2	78385353.9		
Corrected Total	13	913310847.7			

R-Square	Coeff Var	Root MSE	study_sensor_hyper_avg Mean
0.141745	179.1310	8853.550	4942.500

Source	DF	Type I SS	Mean Square	F Value	Pr > F
days_drip	1	22966049.2	22966049.2	0.29	0.6002
study_group	1	105897330.0	105897330.0	1.35	0.2721
days_drip*study_grou	1	593929.3	593929.3	0.01	0.9324

Source	DF	Type III SS	Mean Square	F Value	Pr > F
days_drip	1	9698091.699	9698091.699	0.12	0.7323
study_group	1	8684347.093	8684347.093	0.11	0.7461
days_drip*study_grou	1	593929.292	593929.292	0.01	0.9324



Effect of islet yield on YSI BG Avg and test for interaction

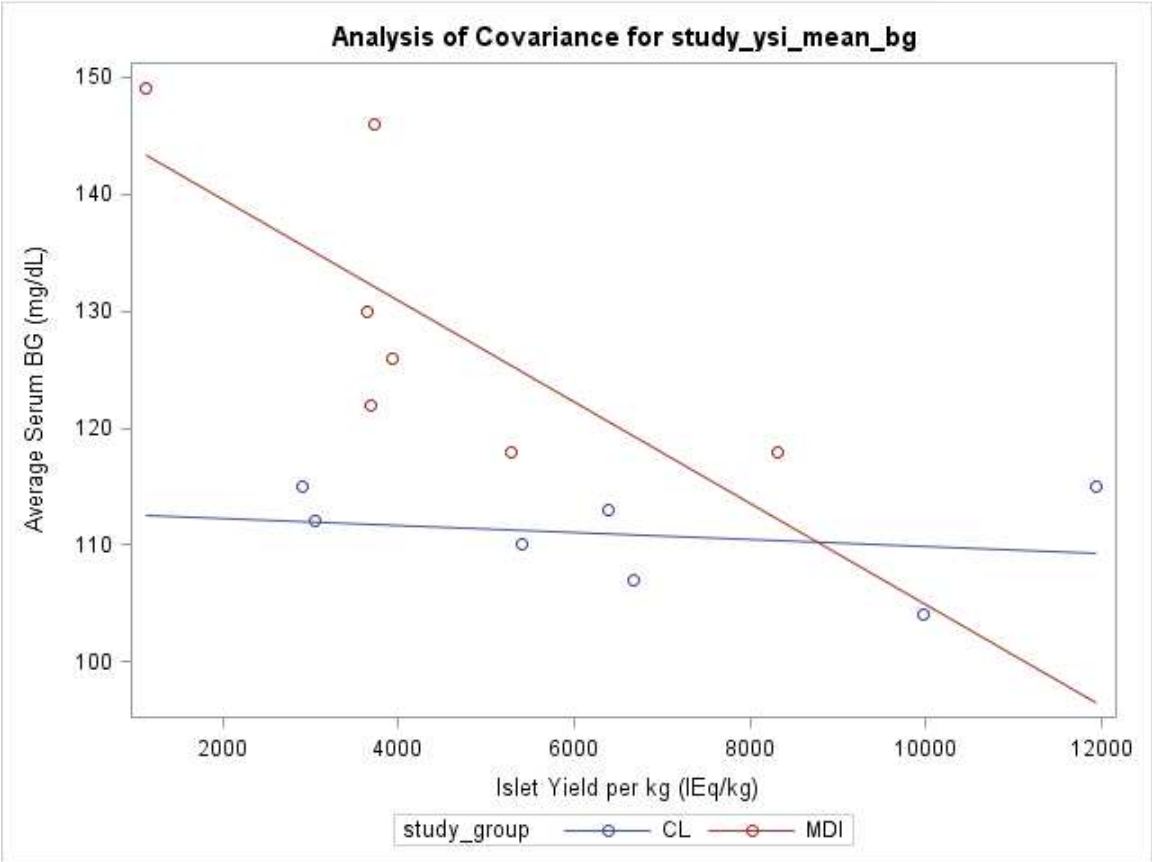
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1803.351731	601.117244	10.97	0.0017
Error	10	547.862554	54.786255		
Corrected Total	13	2351.214286			

R-Square	Coeff Var	Root MSE	study_ysi_mean_bg Mean
0.766987	6.149842	7.401774	120.3571

Source	DF	Type I SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	783.0929889	783.0929889	14.29	0.0036
study_group	1	693.9237203	693.9237203	12.67	0.0052
islet_tx_*study_grou	1	326.3350220	326.3350220	5.96	0.0348

Source	DF	Type III SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	429.3877385	429.3877385	7.84	0.0188
study_group	1	800.9574412	800.9574412	14.62	0.0034
islet_tx_*study_grou	1	326.3350220	326.3350220	5.96	0.0348



Effect of islet yield on YSI BG StDev and test for interaction

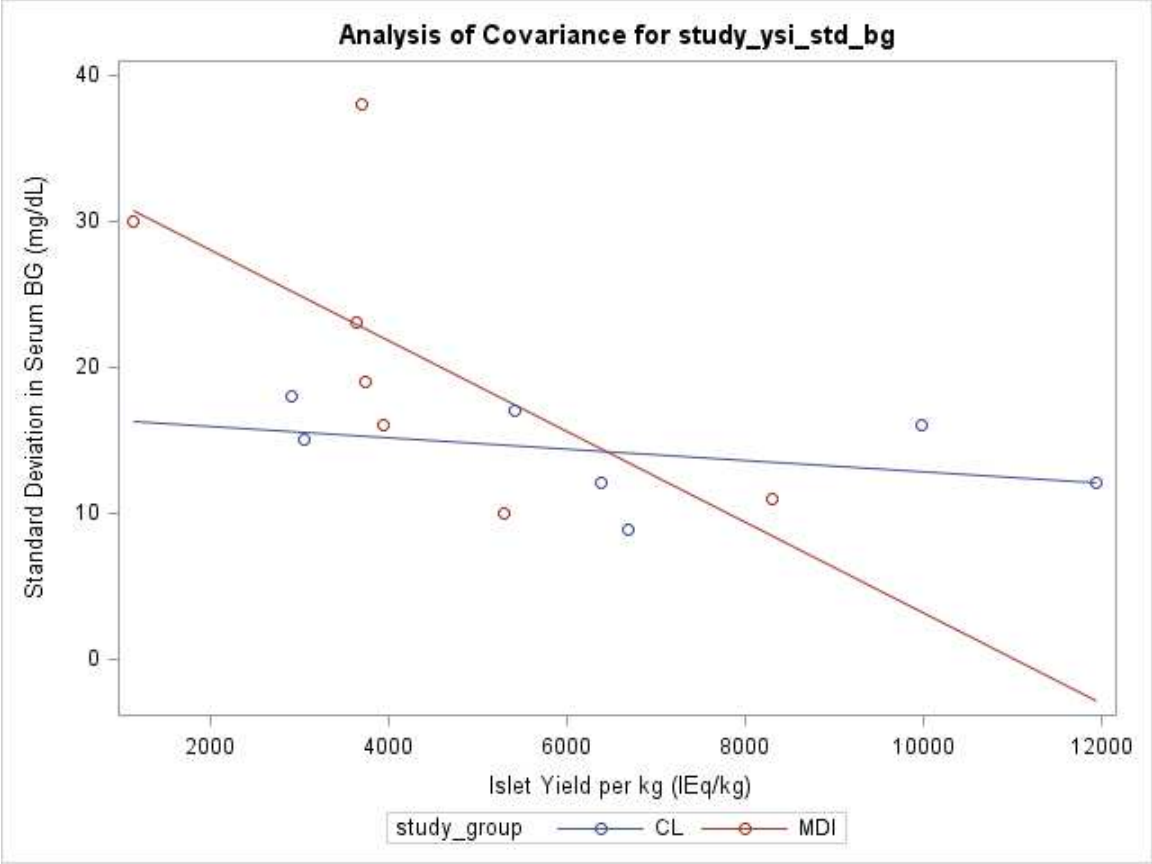
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	449.1376432	149.7125477	3.71	0.0501
Error	10	404.0144997	40.4014500		
Corrected Total	13	853.1521429			

R-Square	Coeff Var	Root MSE	study_ysi_std_bg Mean
0.526445	36.18828	6.356213	17.56429

Source	DF	Type I SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	252.8931113	252.8931113	6.26	0.0313
study_group	1	47.6915576	47.6915576	1.18	0.3028
islet_tx_*study_grou	1	148.5529743	148.5529743	3.68	0.0842

Source	DF	Type III SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	243.3577170	243.3577170	6.02	0.0340
study_group	1	196.0918669	196.0918669	4.85	0.0522
islet_tx_*study_grou	1	148.5529743	148.5529743	3.68	0.0842



Effect of islet yield on Hypoglycemia AUC and test for interaction

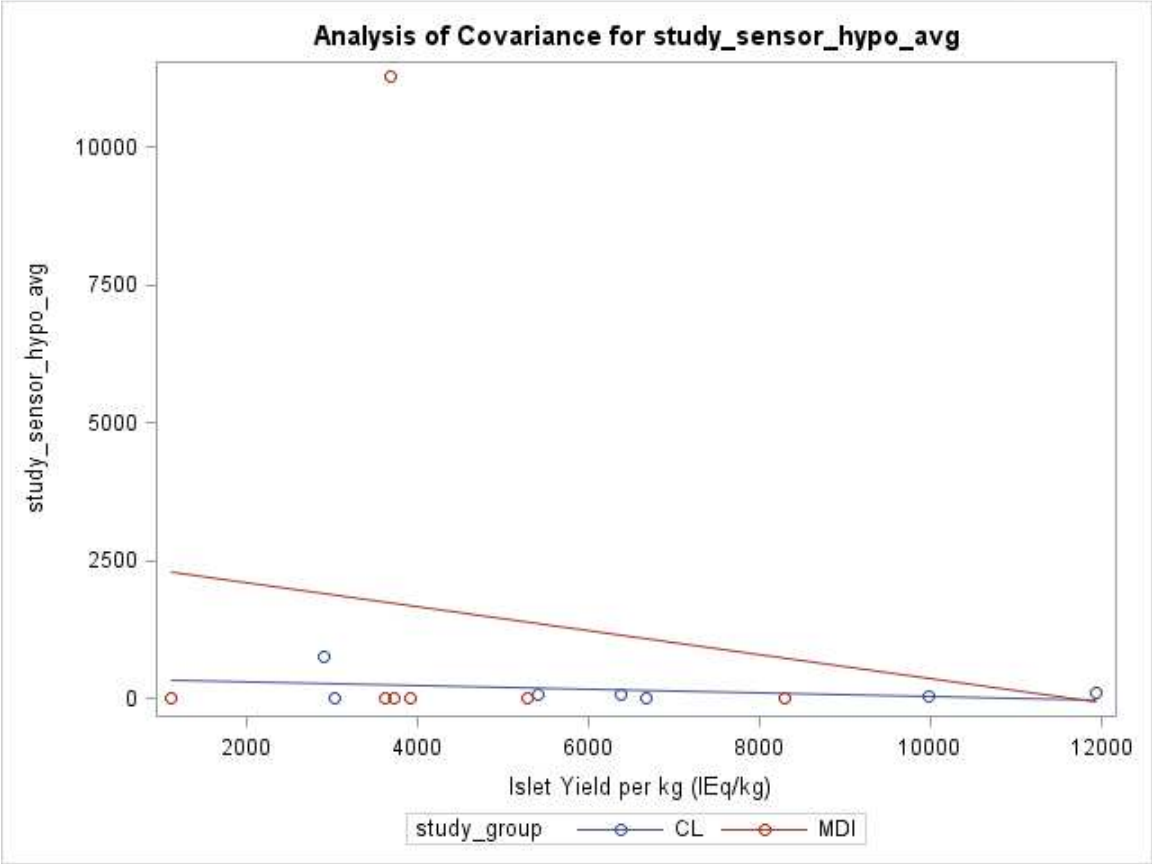
The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	8986301.5	2995433.8	0.28	0.8410
Error	10	108247099.3	10824709.9		
Corrected Total	13	117233400.9			

R-Square	Coeff Var	Root MSE	study_sensor_hypo_avg Mean
0.076653	373.6113	3290.093	880.6190

Source	DF	Type I SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	3693949.109	3693949.109	0.34	0.5720
study_group	1	4604117.325	4604117.325	0.43	0.5290
islet_tx_*study_grou	1	688235.095	688235.095	0.06	0.8060

Source	DF	Type III SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	1273081.237	1273081.237	0.12	0.7387
study_group	1	3021385.115	3021385.115	0.28	0.6088
islet_tx_*study_grou	1	688235.095	688235.095	0.06	0.8060



Effect of islet yield on Hyperglycemia AUC and test for interaction

The GLM Procedure

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	553420846.5	184473615.5	5.13	0.0211
Error	10	359890001.3	35989000.1		
Corrected Total	13	913310847.7			

R-Square	Coeff Var	Root MSE	study_sensor_hyper_avg Mean
0.605950	121.3775	5999.083	4942.500

Source	DF	Type I SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	210818703.4	210818703.4	5.86	0.0360
study_group	1	29202415.4	29202415.4	0.81	0.3889
islet_tx_*study_grou	1	313399727.6	313399727.6	8.71	0.0145

Source	DF	Type III SS	Mean Square	F Value	Pr > F
islet_tx_kg	1	298301510.9	298301510.9	8.29	0.0164
study_group	1	330211745.5	330211745.5	9.18	0.0127
islet_tx_*study_grou	1	313399727.6	313399727.6	8.71	0.0145